Université de Montréal

Association between asthma during pregnancy and postpartum depression

par

Sherief Ahmed

Médicaments et Santé des Populations
Faculté de Pharmacie

Mémoire présenté à la Faculté des études supérieures
en vue de l'obtention du grade de Maîtrise
en Sciences Pharmaceutiques
option Médicaments et Santé des Populations

Décembre 2016

Université de Montréal
Faculté des études supérieures et postdoctorales

Ce mémoire est intitulé :

Association between asthma during pregnancy and postpartum depression

Présenté par :
Sherief Ahmed

a été évaluée évalué par un jury composé des personnes suivantes:

Marie-France Beauchesne PhD, président-rapporteur

Lucie Blais PhD, Directrice de recherche

Gregory Moullec PhD, membre du jury

Résumé

Il a été démontré dans plusieurs études épidémiologiques qu'il existe un risque important de dépression chez les femmes souffrant d'asthme en dehors de la grossesse. Cependant, on en connait peu sur l'association entre l'asthme pendant la grossesse et la dépression post-partum. Par conséquent, le but de cette étude était de quantifier la force de l'association entre l'asthme pendant la grossesse et la dépression post-partum.

À l'aide des bases de données administratives du Québec, nous avons construit une cohorte de 35,520 grossesses de femmes asthmatiques et 197,057 grossesses de femmes non asthmatiques qui ont accouchées entre 1998 et 2009. Les femmes asthmatiques ont été identifiées à l'aide d'une définition opérationnelle validée. Nous avons utilisé la définition de Statistiques Canada pour détecter la dépression post-partum. Cette définition se base sur les codes diagnostics de la dépression enregistrés dans les bases de données de la RAMQ et de MED-ECHO dans l'année suivant l'accouchement. Un modèle d'équations généralisées a été utilisé pour estimer les ratios de cotes (RC) brutes et ajustés et les intervalles de confiance (IC) à 95% entre l'asthme pendant la grossesse et la dépression post-partum. La proportion de femmes ayant eu une dépression post-partum au cours de l'année suivant l'accouchement était plus élevée chez les asthmatiques que chez les non-asthmatiques (6,1% contre 2,9%). Après ajustement pour les variables potentiellement confondantes, nous avons observé que les femmes asthmatiques étaient 58% plus susceptibles de souffrir de dépression post-partum que les femmes non-asthmatiques (RC ajusté : 1,58 ; IC 95%, 1,50 à 1,67).

Les résultats de notre étude suggèrent un risque accru de dépression post-partum chez les femmes asthmatiques. Une attention particulière devrait être accordée aux symptômes dépressifs chez les femmes asthmatiques dans l'année suivant l'accouchement pour détecter la dépression post-partum plus rapidement et intervenir plus efficacement.

Mots-clés : Asthme, grossesse, dépression post-partum, bases de données.

Abstract

There is evidence from several epidemiological studies on the increased risk of depression among women with asthma outside of pregnancy. However, we found no studies designed to investigate the association between asthma during pregnancy and postpartum depression. Therefore, the purpose of this study was to assess the association between asthma during pregnancy and postpartum depression.

Based on Quebec administrative databases, we constructed a cohort of 35,520 pregnancies from asthmatic women and 197,057 pregnancies from non-asthmatic women who delivered between 1998 and 2009. Asthmatic women were identified using a validated operational definition. Postpartum depression was defined and specified with diagnostic codes for depression from the definition of Statistics Canada recorded in the RAMQ or MED-ECHO databases and assessed 1 year postpartum. A generalized estimating equation model was used to estimate the crude and adjusted odds ratios (ORs) of postpartum depression and 95% confidence intervals (CI) comparing women with and without asthma during pregnancy.

The proportion of postpartum depression 1 year after delivery was higher among asthmatic compared to non-asthmatic pregnant women (6.1% vs. 2.9%). After adjusting for potential confounders, we observed that women with asthma were 58% more likely to have postpartum depression (adjusted OR: 1.58; 95%CI, 1.50-1.67) than women without asthma during pregnancy.

The findings of our study suggest an increased risk of postpartum depression among asthmatic women. Attention should be given to depressive symptoms in asthmatic women in the year postpartum to detect postpartum depression more rapidly and intervene more efficiently.

Keywords: Asthma, pregnancy, postpartum depression, databases

Table of contents

List of tables

List of figures

Abbreviations

aOR	Adjusted Odds Ratio
ALSPAC	Avon Longitudinal Study of Parents and Children
BMI	Body mass index
CANMAT	Canadian network for mood and anxiety treatment
CI	Confidence Interval
CES-D	Epidemiologic Studies Depression Scale
cOR	Crude Odds Ratio
cRR	Crude Relative Risk
DAD	Discharge abstract database
EPDS	Edinburgh Postnatal Depression Scale
GC	glucocorticoid resistance
GEE	Generalized Estimating Equations
GPRD	General Practice Research Database
GINA	Global Initiative for Asthma
ICD	International Classification of Disease
IL	Interleukin
ICS	Inhaled corticosteroids
IRR	Incidence rates ratio

LABA	Long-acting beta2-agonists
OHIP	Ontario Health Insurance Plan
OR	Odds Ratio
pOR	Prevalence Odds Ratio
PPD	Postpartum depression
QAPD	Quebec asthma and pregnancy database
RAMQ	Régie de l'Assurance Maladie du Québec
SABA	Short-acting beta2-agonists
TNF-α	Tumor necrosis factor alpha
NHIRD	Taiwan's National Health Insurance Research Database
U.S	United States
WHS	World health survey

To my beloved family and friends

Preface

This MSc thesis consists of seven chapters including an introduction, a review of the literature, the objectives and hypothesis of the study, the methods, the results, discussion and conclusion and research perspectives. A bibliography section follows these chapters.

The introduction chapter provides the rationale and general objective of the study we performed. The review of the literature covers different aspects on the subject of our study with an illustration of the risk factors of postpartum depression while providing an overview of the results relevant to our project together with a focus on asthma during pregnancy and postpartum depression. The objective and hypothesis chapter present the specific goals of our research project. The methodology chapter includes information on the source of data, study design, exposure, outcomes, confounding variables, mediators, statistical analyses performed. The results chapter contains tables reporting the results of our study on the association between asthma during pregnancy and postpartum depression and their interpretation. The discussion chapter presents the strengths and limitations of our project, biological mechanisms of the impact of asthma on depression. Finally, the conclusion and perspective section includes the clinical implications of our results, further research recommendations and it ends with an overall conclusion. The bibliography section contains all articles, books, and reports cited in this thesis.

Acknowledgements

First of all, I am truly grateful to my supervisor, Prof. Lucie Blais, for giving me the opportunity to join her great team, and for providing me with support, advice, and knowledge during my study period. Her guidance throughout my program and her goal-oriented advice helped me gain a rich experience which I appreciate. I would like to thank all the jury members for accepting the evaluation of this project.

I would like to thank Amélie Forget for her exceptional technical help throughout the whole project, and her constructive and precious advice.

I would also like to thank Fatima Kettani and Genevieve Lalonde for sharing their knowledge and experience, and their supporting spirit. I wish to acknowledge also the whole team of Prof. Blais for their magnificent spirit and great friendship.

Lastly, I would also like to thank my parents, whose care and encouragement throughout my whole years of study have been my dearest assets and my brother Tamer for his advice and support during my study.

CHAPTER 1: INTRODUCTION

Introduction

Asthma has been recognized as one of the most common chronic diseases that can complicate pregnancy (1-3). The disease affects about 3.4% to 12.4% of pregnant women and shows an increasing prevalence over time (2-6). Asthmatic women have been found to be at higher risk of adverse pregnancy outcomes than non-asthmatic women in many studies, including preeclampsia, antepartum hemorrhage, hypertensive disorders of pregnancy, caesarean delivery, placenta previa, and postpartum bleeding (2, 3, 7).

Postpartum depression (PPD) is one of the most common mental health problems among women with a prevalence of 10%-15% worldwide (8-10). Previous studies have depicted the feelings and experiences of mothers of postpartum depression such as loneliness, obsessive thinking, loss of control, guilt, insecurities, diminished concentration, fear that life would never be normal again, lack of positive emotions, loss of interests in hobbies or goals, and fear of contemplation of harming themselves and their infants (11, 12). Moreover, postpartum depression has been shown to increase sub-optimal cognitive and infant emotional development (13-16). These episodes begin after delivery and may last one year (17). The period in which postpartum depression is assessed varies considerably between studies (8, 18, 19). Most studies in the literature evaluated postpartum depression at 1 month and 3 months after delivery (20-22). However, according to Canadian guidelines 'Nursing Best Practice Guidelines' in 2005, they stated that the onset of postpartum depression occurs within 1 year postpartum (23). It has been suggested that sociodemographic, social, biological, obstetrical, and personal risk factors are associated with PPD (24).

A recent study showed that depression is an inflammatory disorder due to the increased production of interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α (25). As depression is characterized by immune activation, mainly the innate immune system (26). Sickness behaviour, the emotional and behavioural symptoms that develop as a consequence of acute infection or cytokine therapy, appears to be the result of augmented levels of the pro-inflammatory cytokines interleukin (IL)-1 and tumour necrosis factor (TNF) and is the most commonly cited evidence linking cytokine activation with depression. There is evidence from many epidemiological studies on the increased risk of depression among asthmatics outside of pregnancy, with significant odds ratio ranging between 1.4 and 2.8 (27-29). The biological mechanisms behind this association are still uncertain, but several hypotheses exist. First, the role of cytokines that are known to affect inflammatory responses, and the biological processes they govern may be shared by asthma and depression (30). Second, the exposure to stressful events in the early life and its effects on glucocorticoid resistance (GC) are considered as risk factors for the development of both depression and asthma (31).

Despite the believed association between asthma and depression outside of pregnancy, there is very little literature on the association between asthma during pregnancy and postpartum depression. We found only one study that reported data on this association, but it was designed to explore the impact of the mode and season of delivery on postpartum depression among pregnant women. The findings of this study showed that the odds of postpartum depression within the first 6 months following delivery was higher among pregnant asthmatic women compared to those without asthma during pregnancy, but this difference did not reach statistical

significance (adjusted odds ratio = 1.30 (95% CI:0.98, 1.73) (32). Given the fact that maternal asthma was not the primary exposure, and the association was adjusted for variables that might be in the causal pathway between maternal asthma and postpartum depression, including antepartum depression, early onset of delivery, and poor fetal growth. Such adjustment could have biased the estimate with an underestimation of the impact of maternal asthma on postpartum depression. On the other hand, the authors did not adjust for the area of residence and diabetes mellitus, variables that are known risk factors for postpartum depression.

Thus, the objective of this thesis was to design a study to compare the risk of postpartum depression between pregnant women with and without asthma.

CHAPTER 2: REVIEW OF THE LITERATURE

Review of the literature

This chapter will introduce the definition of asthma and its prevalence and how to manage and treat asthma. In addition, we will discuss asthma during pregnancy, and this will include the impact of asthma during pregnancy and impact of pregnancy on asthma. Moreover, we will present the definition of postpartum depression and its prevalence. Also, we will cover different studies on the association between asthma during pregnancy and postpartum depression, asthma and depression outside pregnancy, depression during pregnancy and postpartum depression. Finally, we will discuss the risk factors of postpartum depression.

2.1 Asthma and its prevalence

Asthma is a complex disorder characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper-responsiveness, and an underlying inflammation (33). According to the Global Initiative for Asthma (GINA) guidelines, asthma is defined as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness and coughing mostly at night or in the early morning. These episodes are usually associated with wide spread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment" (34).

Asthma is a serious global health problem affecting an estimated 300 million individuals worldwide (33, 34). Moreover, noticeably higher estimates can be obtained with less conventional criteria for the diagnosis of clinical asthma (33). The prevalence of asthma has

increased markedly in most countries over the last 50 years especially in westernized societies and is considered as a significant burden not only in terms of health care costs but also in terms of loss of productivity and reduced participation in family life (35, 36). Canada and the United States have the highest prevalence of asthma in the world for both children and adults, reaching about 10% to 11.2% (35, 37). In Quebec, the prevalence of asthma in the population aged 12 and over increased from 8.2% to 9.1% from 2012 to 2014 (38).

2.2 Asthma management and treatment

The target of asthma treatment is to achieve and maintain asthma under control (33). Asthma medications can be classified as controllers and relievers (33). Controllers are drugs which are taken daily to achieve and maintain control of persistent asthma (these medications are also known as long-term preventive, or maintenance medications) and relievers are medications used on an as-needed basis that act rapidly to reverse bronchoconstriction and relieve its symptoms (these medications are also known as acute rescue medications) (33). Acute asthma exacerbations are managed by relievers, while patients with persistent asthma are required to take both classes (33, 34, 39).

2.2.1 Controller medications

Controller medications should be taken daily on a long-term basis to keep asthma under control. The most efficient are those that reduce the underlying inflammation characteristic of asthma (34).

- **Corticosteroids:** Are currently the most potent and effective anti-inflammatory medication available. Inhaled corticosteroids (ICS) have fewer side effects than oral or systemic corticosteroids and are used in the long-term control of asthma (33, 34). ICSs are the most effective long-term controller medications in all levels of persistent asthma, and they have superiority over any other single long-term controller medication (33). The commonly used ICS are Beclomethasone dipropionate, Budesonide, Ciclesonide, Fluticasone propionate, Fluticasone furoate, and Mometasone furoate (33, 34). Systemic corticosteroids are used for a short-term period to treat and achieve a rapid control of the disease (33, 34). Long-term oral corticosteroids therapy (tablets or syrup) are used at the lowest effective dose in cases of severe persistent uncontrolled asthma (see Figure 1), with preferring their termination as soon as asthma control is regained (33, 34).
- **Leukotriene modifiers**: Zafirlukast or Montelukast may be considered an alternative therapy to low doses of inhaled corticosteroids or Cromolyn or Nedocromil for patients with mild persistent asthma. Also as adjunctive therapy in patients not sufficiently controlled by ICSs (see Figure 1) (33). Several studies have demonstrated that leukotriene modifiers are less effective than Long-acting beta2-agonists as add-on therapy (40, 41).
- **Long-acting beta2-agonists (LABA)**: Salmeterol and formoterol are bronchodilators that have a duration of bronchodilation of at least 12 hours after a single dose (33). LABAs are not to be used as monotherapy for long-term control of asthma as they don't have enough effect on the airway inflammation (33). LABA are recommended in combination with ICSs for long-term control in moderate and severe persistent asthma (step 3 to 6 in the stepwise approach to managing asthma, see Figure 1) (33). The

combination of LABA and ICS is the recommended and preferred choice when a low dose of ICS fails to achieve the efficient control of asthma (33, 34).

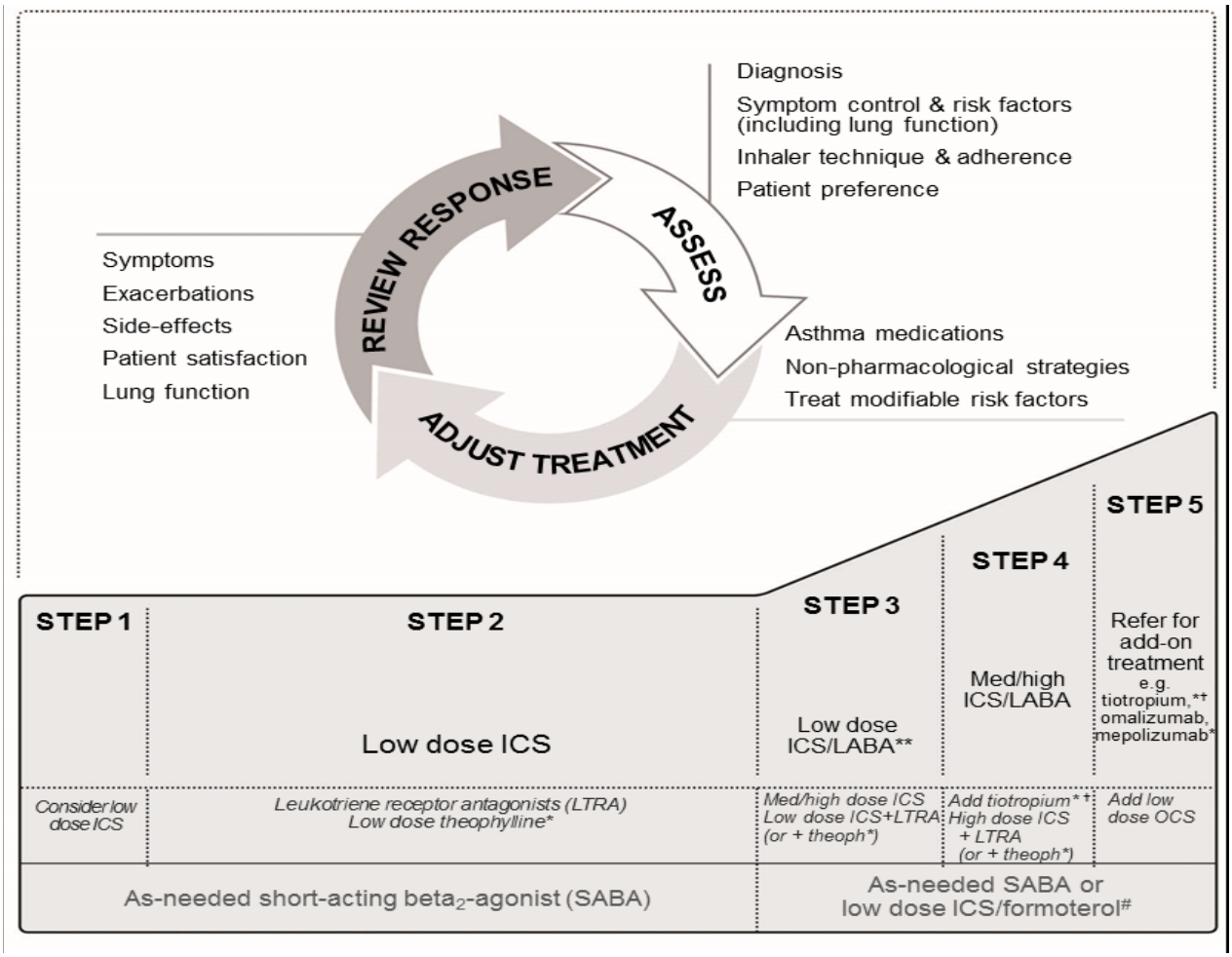
- **Methylxanthines**: Sustained-release Theophylline is a mild-to-moderate bronchodilator used for prevention of symptoms of mild persistent asthma or as adjunctive with ICS, in moderate or persistent asthma (33). Nowadays, they are rarely used in the management of asthma, especially among pregnant women since it can worsen gastric reflux (42).

2.2.2 Relievers

Those are quick-relief medications which are used to treat acute symptoms and exacerbations. They are usually prescribed on an as needed basis (33, 34).

- **Short-acting beta2-agonists (SABA)**: Including Salbutamol, Terbutaline, and Fenoterol, SABAs are considered therapy of choice for relief of acute asthma symptoms, acute exacerbations and preventive of exercise-induced bronchoconstriction prior to exercise (see Figure 1) (33, 34).
- **Anticholinergics**: Ipratropium bromide provides additive benefit to inhaled beta2-agonists in moderate-to-severe asthma exacerbations. They also may be used as an alternative bronchodilator for patients who do not tolerate SABA (33, 34).
- **Systemic corticosteroids**: Short courses of oral corticosteroids or parenteral corticosteroid solutions are used for moderate or severe exacerbations to prevent progression of exacerbation, reverse inflammation, speed recovery, and reduce the rate of relapse (33). They include Prednisone, Prednisolone, and Methylprednisolone (33).

Figure 1. Stepwise approach to asthma treatment in adults according to Global initiative for asthma guidelines (GINA)



Source: Global initiative for asthma guidelines (GINA) for the diagnosis and management of asthma, 2015

2.3 Asthma during pregnancy

Asthma is considered as one of the most frequent chronic diseases complicating pregnancy (1). The prevalence of asthma ranges between 3.4% and 12.4% among pregnant women (1, 4-6). Moreover, a study showed the presence of an overall increasing prevalence of asthma during pregnancy over time (43). In the United States, trends of increased prevalence of asthma have been observed over the past several decades, particularly among younger age groups. These trends suggest a concurrent increase in prevalence in the pregnant population (44, 45).

2.3.1 Impact of asthma on pregnancy

Many studies examined the pregnancy outcomes of asthmatic women compared to non-asthmatic women and had shown increased risk of adverse maternal and fetal outcomes among asthmatic women (2, 4, 7, 46, 47). Asthmatic women were found to be at higher risk of preeclampsia, antepartum hemorrhage, hypertensive disorders, caesarean delivery, placenta previa, and postpartum bleeding compared to non-asthmatic women (2, 4, 7, 46, 47). Adverse fetal outcomes found to be at higher risk among women with asthma are small for gestational age infants, low birth weight, preterm delivery, congenital malformations, transient tachypnea of the newborn, neonatal hypoxia, and neonatal hyperbilirubinemia (7, 48-51).

2.3.2 Impact of pregnancy on asthma

The rule of thirds applies to pregnant asthmatic women, where approximately one-third of the patients suffer from worsening of their asthma symptoms, one-third experience improvement, while one-third of the pregnant women has no change in their asthma (52-54).

Many studies showed that severe asthma is more likely to worsen during pregnancy (7, 55, 56). The fewest symptoms happen after week 37 before delivery, and approximately 75% of women return to their pre-pregnancy status within 3 months postpartum (7). The variation in the course of asthma tends to be consistent during consecutive pregnancies and exacerbations in labor and childbirth are infrequent (7, 39, 56, 57). The mechanism underlying these changes of asthma during pregnancy is still not fully understood. Asthma is a highly variable disease, and a number of physiologic changes exist during pregnancy which could lead to worsening or improve asthma (7, 56). Some physiological factors can improve asthma such as progesterone-mediated bronchodilation and decreased plasma-histamine-mediated bronchoconstriction resulting from increased circulating histaminase (53). On the other hand, increased stress and increased gastroesophageal reflux-induced asthma symptoms are from the factors that may worsen asthma (53). Since the course of asthma can change during pregnancy, therefore pregnant women need to be followed up more closely, and their therapy should be adjusted if necessary to improve and achieve control of symptom (7, 39, 57).

2.4 Postpartum depression and its prevalence

Postpartum depression is a nonpsychotic depressive episode beginning in the postpartum period (58, 59). At present, postpartum depression is not classified as a separate disease; it is diagnosed as part of affective or mood disorders in both the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the World Health Organization's International Classification of Diseases (ICD-10). According to the DSM-IV, postpartum depression is a depressive disorder with onset within the first 4 weeks postpartum. Postpartum depression (PPD) is a significant public health problem, with a prevalence of 10%-

15% worldwide (8-10). In Canada, the prevalence of postpartum depression increased from 8.7% to 16.4% from 2011 to 2014 (60, 61). This condition has negative health implications for the mother, and child (12). The symptoms of postpartum depression are similar to depression unrelated to childbirth (62). However, despite these similarities, postpartum depression is frequently exacerbated by other indicators such as low self-esteem, inability to cope, loneliness, feelings of incompetence, and loss of self (63-65). Moreover, postpartum depression has been shown to increase sub-optimal cognitive and infant emotional development (13-16). The period in which postpartum depression is measured differs between studies (8, 18). Most studies in the literature assessed postpartum depression at 1 month and 3 months after delivery (20-22). However, according to most recent Canadian guidelines 'Nursing Best Practice Guidelines' in 2005, the onset of postpartum depression occurs within 1 year postpartum (23).

2.5 Association between asthma during pregnancy and postpartum depression

There are no published studies specifically designed to investigate the association between asthma during pregnancy and postpartum depression. We found only one case-control study that examined the association between asthma during pregnancy and postpartum depression (PPD) (32), but this study was designed to assess the impact of the mode and season of delivery on postpartum depression, and maternal asthma was considered as a potential confounder. The study subjects consisted of 2,107 cases of postpartum depression and 8,428 controls without postpartum depression selected between 2003 and 2006 from the Taiwan's National Health Insurance Research Database (NHIRD). In this study, mode and season of delivery were considered as the main exposures while asthma was a potential confounder. Postpartum depression was measured within the first 6 months following delivery and identified using

diagnosis codes of depression (ICD-9: 309, 311, 296.2, 296.3, 296.5, 300.4) and the prescription of antidepressants. Among cases and controls, there were 91 and 217 women with asthma respectively. In this case-control study, women with asthma during pregnancy were more likely to have a postpartum depression within the first 6 months following delivery, but this association did not reach statistical significance (odds ratio = 1.3 (95% CI:0.98, 1.73). This study had good external validity since participants come from a national health insurance database which included almost 99% of the total population of Taiwan. However, some limitations should be taken into account in the interpretation of the results. The study was based on health administrative databases that did not include information about possible risk factors of PPD, including lack of social support, family income, education of the mother, area of residence and diabetes mellitus. Not controlling for those variables might have resulted in residual confounding. However, because of the fact that maternal asthma was not the main exposure, the association was adjusted for variables that might be in the causal pathway between maternal asthma and postpartum depression, including antepartum depression, early onset of delivery, and poor fetal. Such adjustment could have biased the estimate of the association between asthma during pregnancy and PPD towards the null.

2.6 Association between asthma and depression outside pregnancy

We identified 10 studies that examined the association between asthma and depression outside pregnancy (27, 29, 66-71). Six of these studies were conducted using a cross-sectional design, and 4 studies were nested case-control and cohort designs. In this section, first I will briefly summarize the main results obtained from the cross-sectional studies followed by the results of nested case-control and cohort studies.

2.6.1 Cross-sectional studies

Trojan et al. (2014) included 12,944 participants aged more than 50 years old, who completed physician-based preventive health examinations at the Cooper Clinic from 2000 to 2012 (27) (Table 1). Asthma was assessed by indicating whether participant ever had a significant problem with any of the symptoms or conditions listed in the questionnaire of the study with asthma as one choice. Asthma diagnosis was then confirmed by a physician based on participant's answers, and current asthma medications were also recorded. Current clinically significant depressive symptoms were measured by the Epidemiologic Studies Depression Scale (CES-D) ≥ 10. The study showed that the prevalence of asthma was 9.0%, but the proportion of patients with CES-D score ≥ 10 by asthma status was not reported. The findings demonstrated that patients with asthma were more likely to have current depressive symptoms than patients without asthma (odds ratio (aOR) =1.41 (95% confidence interval, 1.16-1.70), adjusted for age, female, BMI, diabetes, cancer, hypertension, myocardial infarction, alcohol consumption, cerebral vascular accident, inhaled corticosteroid, long-acting b-agonist and smoking. Similar and consistent findings were reported by all other studies indicating that asthma was associated with depression (29, 66, 67, 69, 70) (Table 1). The majority of these studies used validated measures of both asthma and depression and were characterized by large sample sizes and adequate power to assess the prevalence of depression. These studies were also conducted in different countries and on populations of different age group (adults, and teenagers) and provided consistent results. However, a major limitation of these studies was that they do not allow to assess the temporal association between asthma and depression. They only allow for hypothesis generation and longitudinal studies are warranted.

2.6.2 Nested case-control and cohort studies

Two studies were reported in the literature. Those studies examined the longitudinal association between asthma and depression. First, Walter et al. (2011) published the results of a case-control analysis in a historical cohort using data selected from the General Practice Research Database (GPRD) (68) (Table 1). The authors found that the adjusted incidence rate ratio (IRR) for depression in patients with asthma versus patients without asthma was 1.59 (95%CI: 1.48–1.71) while adjusting for age, sex, practice, diabetes, cardiovascular diseases, cerebrovascular diseases, and smoking. The study has some limitations. There have been no studies that have examined the validity of diagnoses for depression in the GPRD, though a study of psychosis diagnoses using this database found high predictive values (72). Moreover, the authors were unable to assess the severity of asthma directly and had to use a medication based proxy, though this has been used successfully in another study (73). In addition, the authors were unable to measure adherence to medications. Poor adherence may result in fewer visits to a GP because patients would not have to attend to for further prescriptions, or it could lead to poorer asthma control which may in turn result in more visits. Poor compliance may therefore be a residual confounder. The study has some strengths. The authors conducted sensitivity analyses to explore the possible effects of misclassification of depression. There was no loss of follow-up as registration with primary care and exits from the database are carefully recorded. Also, the GPRD has been validated for use in respiratory epidemiology (74), and the results from the database for asthma are consistent with published studies on the epidemiology of asthma (75).

A cohort by Brunner et al. (2014) (71) included 3,016 men and women aged 23–35 years from the United States and followed them for 20 years. The authors found that the hazard of incident depressive symptoms was similar between patients with and without asthma (adjusted hazard ratio = 0.92; 95% CI = 0.70–1.20 while adjusting for age, study center, education, smoking status, and body mass index (BMI)). The major strengths of this study are the ability to examine the temporality of the association between asthma and depressive symptoms over a 20 year period, large sample size, many years of follow-up with good retention, and the availability of data on potential confounders such as obesity and smoking. Nevertheless, The study has limitations. Self-reported provider-diagnosed asthma might lead to non-differential misclassification bias as compared with objective tests. Furthermore, recall bias may misclassify age of onset of disease and erroneously classify pediatric disease on recurrence as incident adult-onset disease.

Van den Bemt et al. (2016) published the results of a case-control analysis in a historical cohort using data from the Continuous Morbidity Registration (CMR) Netherlands database (76) (Table 1). The authors found that the hazard ratio for the first episode of depression in the asthma patients compared to control subjects was not statistically significant, hazard ratio (HRs=1.18, 95% CI: 0.78–1.79) after controlling for months of multi-morbidity. The study has some strengths. The authors used a large primary care cohort with extensive follow-up, with almost 800 patients with asthma and matching numbers of controls based on gender, date of birth and socioeconomic status. Since all residents in the Netherlands are registered in general practice, prevalence and incidence figures based on primary care registrations are representative for the general population. Also, the study had the ability to examine the temporal relation between asthma and depression. Never the less, the study has certain limitations. The authors had no

information on asthma severity, level of asthma control, smoking status and obesity. They may, however, be potential confounders. Patients with frequent exacerbations, moderate-to-severe asthma or uncontrolled asthma may be at higher risk of depression than patients with stable, intermittent-to-mild or controlled asthma. This warrants further investigation. The author used depression as diagnosed by the GP as the outcome of the study. The prevalence of depression is considered to be underestimated because neither all depressed patients present their problem to a GP nor GPs do always diagnose depression when presented (77).

A prospective cohort study by Goodwin et al. (2004), included 2,036 individuals vary between ages 18 and 21 years (78) (Table 1). In this study, the authors have used data gathered during the course of the Christchurch Health and Development Study (CHDS) in New Zealand. Overall, 22.1% of the entire sample was classified as having major depression during the period from 16-18 years, and 23.5% from 18-21 years. The authors found that asthma in adolescence and young adulthood was associated with major depression. Meanwhile, this association was no longer significantly associated after controlling for socio-economic adversity, parental change and conflict, child abuse exposure, and parental adjustment, aOR=1.1 (95%Cl: 0.5-2.1). One important findings of this study is that childhood adversity or unexamined familial factors may account for some of the comorbidity of asthma and depressive and anxiety disorders. The prospective nature of the study allowed to assess the temporality between the onset of asthma and major depression. This study has some limitations. For instance, data on asthma and depression were gathered over relatively wide time intervals i.e. between 16-18 and 18-21 years of age of the participants. It is likely that the study has been subjected to measurement errors due to recall bias. In addition, the reliability of data on asthma diagnosis is questioned because

the study recruited lay interviewers to obtain self-report information on asthma which was not confirmed later with medical diagnosis data.

In summary, although the studies mentioned above share some methodological limitations, they suggest a possible association between asthma and depression among diverse populations.

Table 1. Association between asthma and depression outside of pregnancy.

Articles	Design	Study Population	Source of data	Exposure (asthma)	Outcome (depression)	Result
Trojan et al. 2014 (27)	Cross sectional study	- 12,944 participants aged more than 50 years old.	Questionnaire	Assessed by using a questionnaire to identify whether they had asthma or not.	Measured by Epidemiologic Studies Depression Scale (CES-D).	Patients with asthma were more likely to have current depressive symptoms than patients without asthma (odds ratio (aOR) =1.41 (95% confidence interval, 1.16-1.70), adjusted for age, BMI, diabetes, cancer, hypertension, myocardial infarction, alcohol consumption, cerebral vascular accident, inhaled corticosteroid, long-acting b-agonist and smoking.
Loerbroks et al. 2012 (66)	Cross-sectional study	- 245,727 women and men aged ≥18 years from the 2002 World Health Survey (WHS). - This survey was conducted in 70 countries across five continents (Europe, Australia, South America, Asia and Africa).	Questionnaire	Participants reported physician-diagnosed asthma and episodes of wheezing were assessed by questionnaire within the past 12 months.	The 2002 WHS interview was used to assess the presence of a major depressive episode (MDE) within the previous 12 months.	- The mean prevalence major depressive episode (MDE) in previous 12 months was 8.4%. - Individuals with asthma had higher odds of depression than those without asthma (aOR:2.37, 95% CI:2.10–2.66) while adjusting for age, sex, and education.

Articles	Design	Study Population	Source of data	Exposure (asthma)	Outcome (depression)	Result
DELMAS et al. 2011 (29)	Cross-sectional study	7,000 French teenagers that were interviewed (mean age: 15.1 years) by school doctors/nurses using a standardized questionnaire.	Questionnaire	Assessed by the French version of the standardized International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.	Major depressive episodes (MDE) were assessed by the Composite International Diagnostic Interview short form (CID-SF) during the past 12 months.	- The prevalence of major depressive episodes was 14.2% in teenagers with current asthma versus 9.2% among the others. - Children with current asthma were significantly more likely to have had an episode of MDE in the past year than children who had never had asthma (aOR: 1.7, 95% CI: 1.2–2.4) while adjusting for gender, age, family structure, and the father's employment status.
Goldney et al. 2003 (67)	Cross-sectional study	3,010 participants randomly recruited from South Australian Health Omnibus Survey, aged ≥15 years.	Questionnaire	- Self-reported asthma in past 12 months - The diagnosis was then confirmed by a physician. .	Depression was assessed by the Primary Care Evaluation of Mental Disorders (PRIME-MD) questionnaire.	- There was a statistically significantly higher frequency of major depression among those with asthma (14.4% [43/299]) compared with those without asthma (5.7% [154/2711]; p=0.000). - The prevalence of depression (any level of severity) was higher among individuals with asthma (22.1% (66/299)) than among individuals without asthma (16.7% (452/2711); p-value=0.03).
Scott et al. 2007 (69)	Cross-sectional study	- Eighteen population surveys of household-residing adults were carried out in 17 countries, with a total of 85,088 respondents.	Questionnaire	Asthma was defined by US National Health Interview Survey.	- Mental disorders included anxiety, depressive, and alcohol use disorders. - Assessed with the Composite International Diagnostic Interview (CIDI 3.0).	- The prevalence of major depression varied from 2% to 26% across the surveys. - The pooled age and sex-adjusted OR for depressive disorders among persons with asthma relative to those without asthma was 1.6 [95% confidence interval (95% CI) =1.4, 1.8].

Articles	Design	Study Population	Source of data	Exposure (asthma)	Outcome (depression)	Result
De Miguel Díez et al. 2011 (70)	Cross-sectional study	- 28,966 subjects. - Based on individual data of subjects aged ≥18 years drawn from the 2006 Spanish National Health Survey.	Questionnaire	Participants who have suffered asthma over the previous 12 months and the medical doctor confirmed their asthma diagnosis.	Depression over the previous 12 months, the medical doctor confirmed their depression diagnosis and consumed antidepressant over the last 2 weeks.	- The prevalence of depression was 9% among asthmatics and 5.5% among those without asthma. - OR of 1.39 (95% CI 1.18–1.64) adjusted for sex, age and education.
Walters et al. 2011 (68)	-Historical cohort study. - Followed up through the database for 10 years.	- 11,275 incident cases of asthma aged over 16 years recorded between January 1st, 1995 and December 31st, 1996. - Patients with asthma were matched to patients without asthma by age, sex, and practice (ratio 1:1).	General Practice Research Database.	Defined by Oxford Medical Information System (OXMIS) codes and Read codes to store diagnostic information (Read/OXMIS codes).	Assessed by Oxford Medical Information System (OXMIS) codes and Read codes to store diagnostic information (Read/OXMIS codes).	The adjusted incidence rate ratio (IRR) for depression in patients with asthma versus patients without asthma was 1.59 (95%CI: 1.48–1.71) while adjusting for age, sex, practice, diabetes, cardiovascular diseases, cerebrovascular diseases, and smoking.
Brunner et al. 2014 (71)	Longitudinal observational study	3,016 men and women aged 23–35 years from the United States and followed them for 20 years.	Questionnaire	Having a physician diagnosis of asthma and reporting either asthma symptoms in the past year or current asthma medication use.	Incident depressive symptoms were measured with the Center for Epidemiologic Studies Depression Scale (CES-D) or self-reported antidepressant medication use.	The incident of depressive symptoms was similar between patients with and without asthma (adjusted hazard ratio = 0.92; 95% CI = 0.70–1.20 while adjusting for age, study center, education, smoking status, and body mass index (BMI)).
Van den Bemt et al. 2016 (76)	Historical cohort study	- 795 patients with asthma, 1,033 patients with diabetes and 1,590 matched control subjects. -Based on data from the Continuous Morbidity Registration (CMR) Netherlands database from January 1985 until December 2008. -Patients with an asthma diagnosis were matched to control subjects drawn from the CMR cohort.	Continuous Morbidity Registration (CMR) Database	-Diagnosed since 1985 in the CMR database. -At least one subsequent asthma follow-up visit had to be recorded by the GP after the child's 6th birthday. -Control subjects were free from any of the chronic conditions at the start of their observation period at the age of 18.	Measured by CMR general practitioner after the age of 18.	-Cumulative incidence of depression in asthma patients was 5.2%, in diabetes miletus patients 4.1% and in control subjects 3.3%. -The Hazard Ratio for the first episode of depression in the asthma patients compared to control subjects was not statistically significant, hazard ratio (HRs=1.18, 95% CI: 0.78–1.79) after controlling for months of multi-morbidity.

Articles	Design	Study Population	Source of data	Exposure (asthma)	Outcome (depression)	Result
Goodwin et al. 2004 (78)	Prospective cohort study	-2,036 individuals vary between age 18 and age 21. -Gathered during the course of the Christchurch Health and Development Study (CHDS) in New Zealand.	Questionnaire	Having a physician diagnosis of asthma and reporting either asthma symptoms in the past year.	Assessed by Composite International Diagnostic Interview (CIDI) (WHO 1993) over the periods 16-18 and 18-21 years.	-Overall, 22.1% of the entire sample was classified as having major depression during the period from 16-18 years, and 23.5% from 18-21 years. -Asthma in adolescence and young adulthood was no longer significantly related to major depression, aOR=1.1 (95%Cl: 0.5-2.1) after controlling for socio-economic adversity, parental change and conflict, child abuse exposure, and parental adjustment.

2.7 Association between depression during pregnancy and postpartum depression

Ten prospective cohort studies examined the association between depression during pregnancy and postpartum depression (see Table 2) (20, 79-87). Gaillard et al. (2014) conducted a prospective cohort study between November 2007 and November 2009 and included 264 pregnant outpatients were consecutively enrolled from a single public maternity unit (Louis Mourier Hospital, Colombes, France) (Table 2) (82). Antenatal depression was assessed by the Edinburgh Postnatal Depression Scale (EPDS) between 32 and 41 weeks gestation. Postpartum depression was evaluated by the EPDS during the second month after delivery. Among 264 women, 44 (16.7%) had postpartum depression, and 44 (16.7%) had antenatal depression, as defined by an EDPS ≥12. Moreover, 19 (7.2%) patients presented with both antenatal and postpartum depression symptoms. The authors found that women with antenatal depression were significantly more likely to experience postpartum depression than those without antenatal depression, (OR= 4.6 [95% CI, 2.0–10.1]) after adjusting for age, unemployment, educational level, health insurance, physical abuse by the partner and migrant status. The first strength of this study is the use of a prospective design thus, excluding the possibility of recall bias. Secondly, assessment of depressive symptoms during the second month after delivery, a period of time associated with a high rate of PPD, therefore increasing the statistical power of the study. The study has certain limitations. First, the EPDS is a self-reported questionnaire and may overestimate the rate of PPD as it can neither diagnose depression nor establish prevalence accurately. Secondly, lack of potential confounders that are known to increase the risk of PPD such as social support, life stressors, history of depression and family history of depression.

Another longitudinal study was reported by Heron et al. (2004). This prospective study consisted of 8,323 pregnant women from the Avon Longitudinal Study of Parents and Children (ALSPAC) (Table 2) (85, 88). Depression during pregnancy and postnatal depression were evaluated at 18 and 32 weeks gestation and both 8 weeks and 8 months postpartum with the Edinburgh Postnatal Depression Scale (EPDS). This measure has been shown to be valid in and outside the postnatal period (89). The authors found that depression at 18 and 32 weeks gestation predicted postnatal depression at both 8 weeks and 8 months, after controlling for anxiety at 18 and 32 weeks gestation , with reported OR at 18 weeks of gestation = 3.17 (95% CI: 2.29, 4.37), and OR at 32 weeks of pregnancy = 6.55 (95% CI: 4.68, 9.17), respectively. The study has some limitations. Data of the study were based on self-report only, and there was evidence of selective attrition as individuals who reported the highest initial levels of symptoms were disproportionately likely to drop out of the study. These limitations are offset by major strengths, including the large community sampling frame, prospective design and multiple assessments in the antenatal and postpartum depression.

Another prospective Cohort study (the Maternal Health Study) was performed by Woolhouse et al. (2015). It included 1,507 nulliparous women aged more than 18 years old during the first trimester of pregnancy, collecting data at five postpartum time-points (3, 6, 12, 18 months and 4 years) from six metropolitan public hospitals in Melbourne Australia (Table 2) (83). Depression during pregnancy and postpartum depression at 3, 6, 12 and 18 months and 4 years postpartum were evaluated by the Edinburgh Postnatal Depression Scale (EPDS) ≥13. The authors found that the prevalence of depressive symptoms at 4 years postpartum was 14.5%. This prevalence was higher than at any time-point in the first 12 months postpartum. Strengths

of the study include recruitment of first-time mothers in early pregnancy, an intensive follow-up from early pregnancy to 18 months postpartum, and extension of the study to include follow-up 4 years after the index birth, and very high levels of participant retention. The study has some limitations. Women recruited for the study were not representative in terms of sociodemographic characteristics. Younger women, single women, and women born overseas from a non-English-speaking background were under-represented. Therefore, prevalence estimates of depression likely underestimate the true prevalence of these conditions, and the results presented here may not be fully generalizable. There is also the probability of selective attrition over time in longitudinal studies, where women most at risk of depression are the most likely to be lost to follow-up leading to underestimation of the true prevalence of depression in the population, particularly at later follow-up points.

We mentioned above the most important studies after that we grouped the other studies reported in the literature together because they share common characteristics (see Table 2). We also found similar and consistent findings were reported by all the other studies (20, 79-81, 84, 86, 87). The majority of these studies shared common strengths: based on a population-based prospective cohort designs, a reasonable number of women with postpartum depression symptoms and detailed data for maternal mental health in terms of depressive symptoms during pregnancy, this has allowed robust, concurrent estimates of multiple risk factors. Also, some studies used the structured diagnostic interview to confirm the diagnosis of postpartum depression (81). These studies were also conducted in different countries and provided an insight into the approximate prevalence of PPD. However, these studies suffered from common limitations. They included loss to follow-up which can cause selection bias, residual

confounding due to past history of adversity or mental health problems or due to other unknown social and lifestyle variables. In addition, these studies used the Edinburgh Postnatal Depression Scale (EPDS) (a self-report screening tool) as a measure of depressive symptoms. This measure may be inadequate because it can neither diagnose depression nor establish prevalence accurately. Some of these studies had small sample sizes which would not allow precise estimates of the associations. Also, most of these studies used a convenient sample which may limit the generalizability of the findings.

In summary, the studies mentioned above suggest an association between depression during pregnancy and postpartum depression among different populations.

Table 2. Association between depression during pregnancy and postpartum depression (PPD)

Articles	Design	Study Population	Source of data	Exposure (depression during pregnancy)	Outcome (postpartum depression)	Result
Koutra et al. 2014 (90)	Prospective cohort study	Included 438 pregnant women aged more than 16 years old from four maternity clinics in Greece.	Questionnaires	Assessed by the Edinburgh Postnatal Depression Scale (EPDS) questionnaire at 28-32 weeks of gestation.	Measured by the EPDS at 8 weeks postpartum.	- The authors found that the prevalence of women with probable depression (EPDS score ≥13) was 16.7 % at 28–32 weeks of pregnancy and 13.0 % at 8 weeks postpartum. - Antenatal depression was associated with a 27% increase in the odds of postpartum depression (PPD), (aOR = 1.27, 95 % CI 1.19, 1.36; adjusted for delivery type, infant sex, working during pregnancy, smoking during pregnancy, physical activity before pregnancy and planned pregnancy)
Milgrom et al. 2008 (80)	Prospective cohort study	- 40,333 pregnant women with a mean age of 30.3 years.	Questionnaires	Assessed by the Edinburgh Postnatal Depression Scale (EPDS) questionnaire during pregnancy.	Measured by the EPDS at 6 weeks after childbirth.	- The authors collected antenatal EPDS data from 35,374 women, and 8.9 % of these women had a score >12 indicating major or minor depressive symptoms. - Women with antenatal depression were significantly associated with an increased risk of developing postpartum depression with an adjusted odd ratio of 1.18 (95% CI= (1.15–1.21) controlled for demographic antenatal risk factors and psychosocial antenatal risk factors.
Siu et al. 2012 (81)	Prospective cohort study	805 Chinese pregnant women between 18 and 50 years from nine	Questionnaire	Assessed at the third trimester of pregnancy by the Edinburgh Postnatal	- Evaluated by the EPDS at 2 months after childbirth.	- Among the 805 women who completed the postnatal assessment, 126 (15.7%) were diagnosed with a major

		Maternal and Child Health Centres (MCHCs) for routine antenatal care.		Depression Scale (EPDS) questionnaire.	- Structured Clinical Interview for Diagnostic and Statistical of Mental disorders (DSM-IV) Axis I Disorders (SCID-I) was used to diagnose the presence of major depression in the postnatal period.	depressive episode based on the SCID-I. - Patients with antenatal depressive symptoms were more likely to develop postnatal depression relative to those without antenatal depressive symptoms with an adjusted odds ratio of 4.09 (95% CI: 2.54-6.59) controlled for socio-demographic characteristics.
Gaillard et al. 2014 (82)	Prospective cohort study.	264 pregnant outpatients were consecutively enrolled at a single public maternity unit (Louis Mourier Hospital, Colombes, France).	Questionnaire	Assessed by Edinburgh Postnatal Depression Scale (EPDS) between 32 and 41 weeks gestation.	Evaluated by EPDS during the second month after delivery.	- Among 264 women, 44 (16.7%) had postpartum depression, and 44 (16.7%) had antenatal depression, as defined by an EDPS ≥12. Moreover, 19 (7.2%) patients presented with both antenatal and postpartum depression symptoms. - Women with antenatal depression were more likely to experience postpartum depression than those without antenatal depression, (OR= 4.6 [95% CI, 2.0–10.1]) after adjusting for age, unemployment, educational level, health insurance, physical abuse by the partner and migrant status.
Davey et al. 2011 (20)	Prospective randomized controlled trial of prenatal care.	- 1,403 medically low-risk pregnant women aged 25 years of age or older. - They were recruited through prenatal clinics early in pregnancy.	Questionnaires.	Assessed during the third trimester by Kellner Symptom Questionnaire.	Measured by Edinburgh Postnatal Depression Scale (EPDS) ≥13 at 8 weeks postpartum.	- 11.0% of women displayed symptoms of postpartum depression at eight weeks postpartum. - Pregnant women with depression during pregnancy were more likely to develop major postpartum depression

						compared to those without depression during pregnancy, adjusted OR (95% CI) = 2.83 (1.29–6.19) while controlling for maternal age, having a stable partner, family history of depression, induction of labour, mode of delivery, hospital stay length, sex of baby, alcohol use or binge drinking during pregnancy, and illicit drug use during pregnancy.
Woolhouse et al. 2015 (83)	Prospective Cohort study	1,507 pregnant women aged more than 18 years old, from six metropolitan public hospitals in Melbourne Australia.	Questionnaire	Measured by Edinburgh Postnatal Depression Scale (EPDS).	Measured by (EPDS)≥13 at 3, 6, 12 and 18 months and 4 years postpartum.	The authors found that the prevalence of depressive symptoms at 4 years postpartum was 14.5%, and was higher than at any time-point in the first 12 months postpartum.
Lee et al. 2007 (84)	Prospective longitudinal study.	357 pregnant women aged more than 18 years of age recruited in an antenatal clinic of a regional hospital in Hong Kong.	Questionnaire	Measured by the Hospital Anxiety and Depression Scale at first trimester, second trimester, and third trimester.	Evaluated by the Edinburgh Postnatal Depression Scale questionnaire at 6 weeks postpartum.	- The authors found that 24.2 % of women who completed the 6-week postpartum questionnaire scored above threshold on the Edinburgh Postnatal Depression Scale, representing a high potential of having clinically significant postpartum depression. - Women with antenatal depression were more likely to develop postpartum depression than those without antenatal depression, adjusted OR 4.16, 95% CI 2.05–8.46 in the first trimester; adjusted OR 3.35, 95% CI 1.62–6.91 in second trimester; and adjusted OR 2.67, 95% CI 1.27–5.58 in third trimester controlling for age, parity, marital status, educational level, family

						income, history of smoking and history of drinking.
Heron et al. 2004 (85)	Prospective longitudinal study	8,323 pregnant women based on Avon Longitudinal Study of Parents and Children (ALSPAC).	Questionnaire	Evaluated at 18 and 32 weeks gestation with the Edinburgh Postnatal Depression Scale (EPDS).	Assessed at both 8 weeks and 8 months postpartum with the Edinburgh Postnatal Depression Scale (EPDS).	Antenatal depression predicted postnatal depression at both 8 weeks and 8 months, even after controlling for antenatal anxiety, with reported OR at 18 weeks of gestation = 3.17 (95% CI: 2.29, 4.37), and OR at 32 weeks of pregnancy = 6.55 (95% CI: 4.68, 9.17), respectively.
Park et al.2015 (86)	Longitudinal study	- 153 Korean women aged 18 years and older. - Participants were recruited from three maternity clinics in Korea.	Questionnaire	Assessed by the Edinburgh Postnatal Depression Scale Korean at first, second (24-26 weeks), third (32 -34 weeks) trimester.	Evaluated by the Edinburgh Postnatal Depression Scale Korean at 4 weeks postpartum.	- The prevalence of depression in the prenatal and postpartum period ranged from 40.5% to 61.4%. - Only depression at the second and third trimester was significantly associated with an increased risk of developing postpartum depression at 4 weeks after childbirth, ($p<0.01$). However, depression at the first trimester was not associated with developing post-partum depression.
Hamdan et al.2011 (87)	Prospective study	- 137 pregnant women, aged 18 and above. - These women were attending the Maternal and Child Health Center (MCHC) in the Emirate of Sharjah.	Questionnaire	Assessed during the second and third trimester of pregnancy by the Beck Depression Inventory-II (BDI-II).	Measured by the Edinburgh Postnatal Depression Scale (EPDS) and Mini International Neuropsychiatric Interview (MINI) at 2 months and 4 months.	- The prevalence of postpartum depression for women in this study was 10%. - Depression during pregnancy in both the second and third trimesters was significantly associated with postpartum depression at 2 and 4 months after childbirth, ($p<0.01$ and $p<0.002$, respectively).

2.8 Risk factors of postpartum depression

From the literature, we identified the risk factors for postpartum depression. The causes of the postpartum depression remain unclear, but several risk factors have been determined, these risk factors are categorized into sociodemographic variables, maternal characteristics before and during pregnancy, delivery specifications, maternal characteristics after childbirth and infant characteristics (see Table 3). Table 3 represents the risk factors for postpartum depression and an estimated crude and adjusted odd ratios or relative risks of PPD. It also shows whether these risk factors can be measured from data recorded in the Quebec administrative databases.

Table 3. Risk factors of postpartum depression.

Risk factors	Range of crude OR (cOR)	Range of adjusted OR (aOR) / Relative risk (RR) of postpartum depression (references)	Information available in the Quebec administrative databases
Socio-demographic factors			
Younger maternal age		aOR: 1.14-5.27 (22, 91, 92)	yes
Residential area		Rural vs. Urban aOR= 0.80 (95% CI: 0.57–1.11) (93)	yes
Mother education		Only reading and writing vs. University aOR= 2.20 (95% CI: 1.33–3.61) (91) Primary/High school vs. University aOR= 1.71 (95% CI: 1.04–2.83) (91) No education vs. College aOR= 2.08 (95% CI: 1.39–3.11) (24)	no
Husband education		No education vs. College aOR= 1.80 (95% CI: 1.03–3.13) (24) Primary school vs. College aOR= 1.40 (95% CI: 1.08–1.81) (24)	no
Unemployment	cOR= 2.6 (95% CI: 1.5–4.7) (94)		no
Financial problem		aOR= 1.13 (95% CI: 1.07-1.20) (95) aOR=1.82 (95% CI: 1.22–2.76) (96)	no
Public insurance welfare		In New York state (excluding New York City) Public insurance vs. Private aOR= 3.8 (95% CI: 3.5–4.1) (97) In New York City Public insurance vs. Private aOR= 2.1 (95% CI: 1.8–2.5) (97)	yes
Domestic violence		aOR= 2.82 (95% CI: 1.15-6.89) (98)	no

Risk factors	Range of crude OR (cOR)	Range of adjusted OR (aOR) / Relative risk (RR) of postpartum depression (references)	Information available in the Quebec administrative databases
		aOR= 4.0 (95% CI: 1.6–10.2) (99)	
Childhood physical abuse		aOR= 1.69 (95% CI: 1.04-2.75) (21)	no
Lack of social support by the partner		aOR= 1.9 (95% CI: 1.2-3.1) (100) aOR= 3.65 (95% CI: 1.22–5.21) (96)	no
Lack of social support by the family		aOR= 4.34 (95% CI: 2.70–6.13) (96)	no
Poor marital relationship		aOR= 1.83 (95% CI: 1.32–2.65) (96)	no
Polygamy		aOR= 7.7 (95% CI: 2.3-25.9) (101)	no
Maternal characteristics before pregnancy			
History of miscarriage		1-2 vs. 0 aOR= 1.31 (95% CI: 1.05–1.62) (24) +3 vs. 0 aOR= 2.40 (95% CI: 1.30–4.43) (24)	yes
Premenstrual syndrome		aOR= 1.5 (95% CI: 1.1-2.1) (100) aOR= 1.82 (95% CI: 1.51–2.20) (24)	yes
Maternal diabetes		aOR= 1.69 (95% CI: 1.27-2.23) (102)	yes
History of anxiety		aOR = 2.79 (95% CI: 1.69, 6.67) (103)	yes
History of depression		aOR: 2.4-5.1 (21, 101, 104-106)	yes
History of mental illness		aOR = 4.48 (95% CI: 3.32–6.04) (24) aOR = 5.6 (95% CI: 1.1–28.0) (99)	yes
Family history of mental illness	cOR = 2.53 (95% CI: 1.43–4.5) (107) cOR= 3.64 (95% CI: 1.68-7.86) (108)		no
History of postpartum depression		aOR = 6.1 (95% CI: 1.8-20.4) (109)	yes
Parity		Primiparity aOR= 1.49 (95% CI: 1.10–2.03) (96) Multiparity aOR= 1.59 (95% CI: 1.22–2.08) (22)	no
Maternal characteristics during pregnancy			
Depression		aOR: 1.18-6.55 (20, 79-83, 85)	yes

Risk factors	Range of crude OR (cOR)	Range of adjusted OR (aOR) / Relative risk (RR) of postpartum depression (references)	Information available in the Quebec administrative databases
Anxiety		aOR: 1.47-4.99 (20, 79, 85, 110, 111)	yes
Anemia		aOR= 4.64 (95% CI: 1.33-16.08) (112) aOR = 1.32 (95% CI: 1.08-1.60) (32)	yes
Weight gain during pregnancy		aOR= 1.48 (95% CI: 1.03-2.12) (113)	no
Gestational diabetes		aOR= 1.96 (95% CI: 1.27-3.04) (102)	yes
Pre-eclampsia		aOR= 3.62 (95% CI: 1.05–9.74) (114)	yes
Hyperemesis gravidarum	cOR= 4.49 (95% CI: 1.41, 14.29) (115)		yes
Alcohol use	First trimester cOR= 4.90 (95% CI: 2.76-8.68) (116) Second trimester cOR= 10.10 (95% CI: 3.67-27.75) (116) Third trimester cOR= 3.50 (95% CI: 1.32-9.28) (116)		no
Smoking		aOR= 1.4 (95% CI: 1.1–1.8) (117)	no
Unplanned pregnancy		aOR: 1.56-2.11 (24, 96, 98)	no
Heart diseases		aOR= 2.51 (95% CI: 1.94-3.24) (32)	yes
Epilepsy		aOR= 3.39 (95% CI: 1.20-9.56) (32)	yes
Delivery characteristics			
Early onset of delivery (premature labor)		aOR= 1.95 (95% CI: 1.22-3.14) (32)	yes
Preterm birth (< 37 weeks of gestation)		aOR=1.65 (95% CI: 1.08-2.56) (105)	yes
Mode of delivery		Caesarean section vs. vaginal delivery aOR=1.38 (95% CI: 1.08-1.77) (105)	yes
Season of delivery		Spring vs. winter aOR=0.88 (95% CI: 0.77-1.01) (32) Summer vs. winter aOR= 0.61 (95% CI: 0.53-0.70) (32)	yes

Risk factors	Range of crude OR (cOR)	Range of adjusted OR (aOR) / Relative risk (RR) of postpartum depression (references)	Information available in the Quebec administrative databases
		fall vs. winter aOR=0.65 (95% CI: 0.56-0.74) (32)	
Maternal characteristics after childbirth			
Subinvolution of uterus		aOR= 2.13 (95% CI: 1.25-3.63) (32)	yes
Urinary tract infection		aOR= 1.88 (95% CI: 1.61-2.21) (32) aOR= 1.85 (95% CI: 1.08–3.16) (22)	yes
Difficulty of breastfeeding		aOR= 2.98 (95% CI: 1.20-7.43) (98)	no
Postpartum anemia		aOR=1.70 (95% CI: 1.05–2.74) (8)	no
Postpartum haemorrhage		aOR= 1.37 (95% CI: 1.04-1.80) (32)	no
Infant characteristics			
Low birth weight (≤ 2500g)		RR= 2.1 (95% CI: 1.3-3.3) (118)	yes
Poor fetal growth		aOR= 1.35 (95% CI: 1.03-1.78) (32)	yes
≥5 Diarrheal episodes per year		RR= 2.4 (95% CI: 1.7-3.3) (118)	no
Perinatal death		aOR= 14.1 (95% CI: 2.5–78.0) (99)	yes
Stillbirth		aOR= 13.65 (95% CI: 1.74–106.94) (119)	yes
Temperamental difficult child		aOR= 1.9 (95% CI: 1.3-2.7) (100)	no
Insufficient baby cares after delivery (inadequate baby care facilities)		aOR= 1.45 (95% CI: 1.15–1.84) (24)	no
Baby physical problems		aOR= 2.27 (95% CI: 1.15-4.49) (92)	no
Congenital malformations		aOR= 1.67 (95% CI:1.15-2.42) (105)	yes

CHAPTER 3: OBJECTIVES & HYPOTHESIS

3.1 Primary objective

To compare the risk of postpartum depression in the year following delivery between pregnant women with and without asthma.

3.2 Secondary objective

1. To compare the risk of postpartum depression at 1 month and 3 months following delivery between pregnant women with and without asthma.

2. To investigate the association between maternal asthma and postpartum depression among women with and without depression or postpartum depression 10 years prior to pregnancy.

3.3 Hypothesis

The incidence of postpartum depression will be higher among women with asthma than women without asthma.

CHAPTER 4: METHODS

4.1 Source of data

We used the Quebec asthma and pregnancy database (QAPD) as the source of data. This database has been previously used to examine the link between the use of asthmatic medications during pregnancy and the risk of congenital malformations (120, 121). Briefly, the QAPD was built from the linkage of two administrative health databases in the province of Quebec (Canada): the Régie de l'assurance maladie du Québec (RAMQ) and the Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (MED-ECHO) database. The RAMQ database includes mainly two types of data: (1) data on medical services provided to all residents of Quebec and (2) data on prescription medications dispensed in community pharmacies for residents covered by the RAMQ's Public Drug Insurance Plan around 42% of the residents of Quebec (welfare recipients, employees who have no access to a drug plan from their employer or spouse's employer, and individuals 65 years of age or older). The MED-ECHO database contains data on acute care hospitalizations and covers all the inhabitants of Quebec.

The QAPD includes all women who delivered in a hospital between January 1, 1990, and March 31, 2010, and who had at least one asthma diagnosis recorded in the RAMQ or MED-ECHO databases in the 2 years prior to one or more of their deliveries, plus a fourfold larger random sample of other women who delivered during the same period (120). By using gestational age at birth and date of birth of the newborns, we retrospectively identified the date of the first day of the last menstrual period and the date of delivery for each pregnancy using validated algorithms (122). The validity of the variables was assessed by calculating Pearson correlation coefficient between the values obtained from the databases and patients' medical charts, and the correlations

were found to be high for all variables ranging from 0.920 to 0.999. We had access to data related to hospitalizations and to medical services dispensed between January 1988 and March 2010 for all pregnant women and their newborns.

4.2 Study design

A population-based cohort design was used to conduct the study. The cohort was selected from the QAPD, which includes all pregnancies from women with asthma and all pregnancies from a random sample of women without asthma selected between January 1, 1990, and March 31, 2010, and identified from the delivery hospitalization recorded in the MED-ECHO database, independently of the drug insurance plan. The cohort inclusion criteria were as follows: (1) a pregnancy with a delivery that occurred in a hospital between January 1998 and March 2009, so that at least 1 year of follow-up data after delivery and 10 years of data prior to pregnancy were available for the mothers; (2) a gestational period between 20 and 45 weeks; (3) women aged between 15 to 45 years old at the beginning of pregnancy; and (4) pregnancies from asthmatic and non-asthmatic women, as operationally defined in the next section. We excluded from the cohort: (1) women with a diagnosis of chronic bronchitis, emphysema, chronic airway obstruction, tuberculosis, bronchiectasis, lung cancer and cystic fibrosis recorded in the RAMQ or MED-ECHO databases in the 2 years prior to delivery; (2) women who died the day of delivery; and (3) women who delivered but for whom no information was available about their newborns. Pregnant women were followed from the day of delivery until the first of the following events: (1) the date of first diagnosis of postpartum depression; (2) death from any cause; (3) the end of follow-up which was 365 days postpartum; (4) the end of the study period, i.e. March 31, 2010; or (5) the beginning of a new pregnancy.

4.3 Women with and without asthma

Women with asthma were identified with the following validated operational definition: at least one hospitalization with a primary, admission or secondary diagnosis of asthma (International Classification of Disease (ICD) diagnostic codes for asthma:ICD-9: 493, except 493.2, or ICD-10: J45) recorded in the MED-ECHO database or at least two medical claims with an asthma diagnosis registered in the RAMQ database within two consecutive years since 1988 until delivery (123). This operational definition had a sensitivity of 80.6% and a specificity of 81.4% comparing Ontario Health Insurance Plan (OHIP) database with primary care practitioner chart diagnosis. (123). Also, asthma diagnoses recorded in the RAMQ database have been validated against medical chart and found to be accurate (50, 124), with a sensitivity of 85% and a specificity of 95% for patients 16-44 years old (124). In addition, to verify that asthma was still present during pregnancy, women had to have at least one diagnosis of asthma recorded in the RAMQ or MED-ECHO databases in the two years before delivery. Women with no diagnosis of asthma from 1988 until delivery were identified as non-asthmatics.

4.4 Postpartum depression

Cases of postpartum depression were identified using the definition of Statistics Canada, i.e. at least one diagnosis of depression (ICD-9: 296.2, 296.3, 300.4, 311; and ICD-10: F32-F33, F34.1, F38.1) (please see the specific definitions for each code of ICD-9 and ICD-10 in Table 4) recorded in the RAMQ or MED-ECHO databases (125). The operational definition based on ICD-9 codes had a sensitivity of 28.93% and a specificity of 99.66%, while the sensitivity was 34.17% and the specificity was 99.55% for ICD-10 codes comparing discharge abstract database (DAD) with chart review extracted by two trained chart reviewers with nursing backgrounds (126).

Moreover, as we saw in the literature review, the period in which postpartum depression is assessed varies between studies (8, 18). Most studies in the literature evaluated postpartum depression at 1 month and 3 months after delivery (20-22). However, according to Canadian guidelines 'Nursing Best Practice Guidelines' in 2005, they stated that the onset of postpartum depression occurs within 1 year postpartum (23). In the present study, we used three different time periods to evaluate postpartum depression: 1 year postpartum was considered as the primary outcome, while 1 month and 3 months postpartum were used as secondary outcomes.

Table 4. Definitions of postpartum depression based on ICD-9 and ICD-10 codes

ICD-9 code	ICD-10 code	Label of the code
296.20	F32.9	Major depressive disorder, single episode unspecified
296.21	F32.0	Major depressive disorder, single episode- mild
296.22	F32.1	Major depressive disorder, single episode moderate
296.23	F32.2	Major depressive disorder, single episode severe, without mention of psychotic behavior
296.24	F32.3	Major depressive disorder, single episode severe, specified as with psychotic behavior
296.25	F32.4	Depressive disorder, single episode, in partial remission
296.26	F32.5	Depressive disorder, single episode, in full remission
296.30	F33.9	Major depressive disorder, recurrent episode unspecified
296.31	F33.0	Major depressive disorder, recurrent episode mild
296.32	F33.1	Major depressive disorder, recurrent episode moderate
296.33	F33.2	Major depressive disorder, recurrent episode severe, without mention of psychotic behavior
296.34	F33.3	Major depressive disorder, recurrent episode severe, specified as with psychotic behavior
296.35	F33.41	Major depressive disorder, recurrent episode in partial or unspecified remission
296.36	F33.42	Major depressive disorder, recurrent episode in full remission
	F33.8	Recurrent depressive disorder, other
300.4	F34.1	Dysthymic disorder
	F38.1	Other recurrent mood disorders
311	F32.9	Depressive episode, unspecified

4.5 Confounding variables and mediators

From the literature, we identified the risk factors for postpartum depression (please see Table 3 in the literature section), and we classified them as either potential confounders or potential mediators. Confounding is mixing of the effect of the exposure under study on the outcome with that of a third factor that is associated with the exposure, an independent risk factor for the disease, and not in the causal pathway between exposure and disease (127-129). In contrast, a mediation effect occurs when the third variable (mediator, M) carries the influence of a given independent variable (X) to a given dependent variable (Y) (130). Therefore, potential mediators could be in the causal pathway between exposure and outcome. Potential confounders include maternal age (15-17, 18-25, 26-35 and 36-45 years) (22, 32, 91, 92, 96, 131, 132), the area of residence (rural/urban) (93), and drug insurance plan (public with social welfare, public without social welfare and private at the beginning of pregnancy (97). We also considered previous miscarriage in the 10 years prior to pregnancy (yes/no) (24), history of depression or postpartum depression in the 10 years prior to pregnancy (yes/no) (21, 101, 104, 109) and the occurrence of at least 1 delivery as a proxy of parity (≥ 1 previous pregnancy/no previous pregnancy) in the 10 years prior to pregnancy, as well as anxiety (yes/no) (103), other psychiatric disorders (schizophrenia, bipolar, psychotic and personality disorders: yes/no) (24, 99), diabetes mellitus (yes/no) (102), heart disease (yes/no) and epilepsy (yes/no) in the year prior to pregnancy. Finally, we assessed season of delivery (winter, autumn, spring, and summer) (32). Also, we did not have information on the other potential risk factors that are listed in Table 3 in the literature review, because those variables are not recorded in the Quebec administrative databases. Therefore, these factors were not taken into consideration in our analyses. The impact of residual confounding due to unmeasured potential confounders will be explained later in the discussion section. Moreover, we did not

consider using medications for asthma or depression in our analysis as we have only information on pharmaceutical services of public but not private drug insurance, which constitutes about 40% of the population. Therefore, we decided to include all pregnancies of women with asthma regardless of their drug insurance plan to maintain the representativeness of the study population.

Potential mediators include depression during pregnancy (20, 79-83, 85), anxiety during pregnancy (20, 79, 85, 110, 111), anemia during pregnancy (32, 112), gestational diabetes (102), pre-eclampsia (114), hyperemesis gravidarum (115), preterm birth (< 37 weeks of gestation) (105), mode of delivery (105), poor fetal growth (32), stillbirth (fetal loss ≥20 weeks of gestation) (119), low birth weight (≤2500g) (118) and congenital malformations identified at delivery (105). Mediators were not adjusted for in the analyses as it could have underestimated the association between asthma during pregnancy and postpartum depression (133).

4.6 Statistical analysis

Proportions were used to compare women's characteristics with and without asthma during pregnancy. We also compared the proportion of women with postpartum depression between women with and without asthma during pregnancy, using our three pre-specified periods (1 month postpartum, 3 months postpartum, and 1 year postpartum). We used generalized estimating equation (GEE) models with a logistic link and an exchangeable correlation matrix to estimate the crude and adjusted odds ratios (ORs) of postpartum depression and 95% confidence intervals (CI) comparing women with and without asthma during pregnancy (134). Adjusted ORs were estimated with models including potential confounders such as maternal age (15-17, 18-25, 26-35 and 36-45 years), the area of residence (rural/urban), drug insurance plan (public with social

welfare, public without social welfare and private at the beginning of pregnancy as well as previous miscarriage in the 10 years prior to pregnancy (yes/no), history of depression or postpartum depression in the 10 years prior to pregnancy (yes/no) and the occurrence of at least 1 delivery as a proxy of parity (≥ 1 previous pregnancy/no previous pregnancy) in the 10 years prior to pregnancy. In addition, we adjusted for anxiety (yes/no), diabetes mellitus (yes/no), heart disease (yes/no) and epilepsy (yes/no) in the year prior to pregnancy and finally, we controlled for the season of delivery (winter, autumn, spring, and summer). One model was used for each of the three periods in which postpartum depression was assessed. GEE models were used to take into account the correlation between the consecutive pregnancies of a woman (135) since women could contribute more than two pregnancies during the study period. Moreover, stratified analyses were performed to assess the association under study separately for women with and without depression or postpartum depression 10 years before the current pregnancy. A GEE model including an interaction term between maternal asthma and depression or postpartum depression in the 10 years before pregnancy was used to test whether or not a history of depression was an effect modifier of the association between asthma during pregnancy and postpartum depression. Finally, a secondary analysis was carried out to investigate the association between maternal asthma and postpartum depression among women without depression or postpartum depression 10 years prior to pregnancy and without depression during pregnancy. Analyses were conducted with the SAS 9.3 software (SAS Institute, Cary, NC, USA).

4.7 Sample size and power

The study cohort included 232,577 pregnancies (35,520 from women with asthma and 197,057 from women without asthma).

Assuming an alpha error of 5%, and considering the prevalence of postpartum depression in the year following delivery to be 6.1%, we assumed to have a power of 90% to detect an odds ratio of 1.12 for women with asthma against women without asthma.

4.8 Ethics approval

This research project was approved by the Ethics Committee of the *Hôpital du Sacré-Coeur de Montréal*. Authorization was obtained from the *Commission d'accès à l'information du Québec* before the information from the RAMQ and MED-ECHO databases was accessed and linked.

CHAPTER 5: RESULTS

Results

We started with 583,071 pregnancies in the QAPD and kept only those who delivered between 1998 and 2009 (52.6%). Of these, 24.1 % met the exclusion criteria. Finally, the study cohort included 232,577 pregnancies (35,520 from women with asthma and 197,057 from women without asthma) that reached the 20th week of gestation and delivered between January 1998 and March 2009 (please see the flow chart in Figure 2).

Table 5 presents the characteristics of the pregnancies among women with and without asthma during pregnancy. Overall, women with asthma were more likely to be younger than 25 years of age, to reside in an urban area and to have public drug insurance than women without asthma. The prevalence of heart disease, epilepsy, and diabetes mellitus, as well as anxiety and other psychiatric disorders in the year prior to pregnancy were higher among women with asthma than women without asthma. Moreover, women with asthma were more likely to have had depression or postpartum depression and a history of miscarriage in the 10 years prior to pregnancy. Women with asthma were also more likely to have depression during pregnancy, anxiety during pregnancy, anemia during pregnancy, gestational diabetes, preeclampsia, and hyperemesis gravidarum. We also found that the proportion of women who had a preterm birth, caesarean delivery, an infant with low birth weight or with poor fetal growth or an infant with a congenital malformation at delivery were greater among women with asthma. We found, however, no difference in the proportion of stillbirths between the two groups.

Table 6 shows the characteristics of women with and without asthma stratified by the presence or absence of a history of depression or postpartum depression in the 10 years prior to current

pregnancy. Very similar distributions of maternal age, living in urban area, and drug insurance plan type were seen in the four subgroups of pregnancies with or without depression or postpartum depression in the 10 years prior to the current pregnancy (see Table 6), except that the prevalence of heart disease, epilepsy, diabetes mellitus, anxiety and other psychological disorders, as well as pregnancy complications, was higher in the subgroups of women with history of depression or postpartum depression compared to women without depression or postpartum depression in the 10 years before pregnancy (see Table 6).

Crude analyses presented in Table 7 shows that the proportion of pregnant women who had a postpartum depression was higher among women with asthma compared to women without asthma at 1 month postpartum (0.8% vs. 0.4%), 3 months postpartum (2.0% vs. 1.0%,) and 1 year postpartum (6.1% vs. 2.9%).

The Generalized Estimating Equation (GEE) model (Table 8) that included all measurable potential confounders showed that maternal asthma during pregnancy was significantly associated with an increased risk of 1-year postpartum depression (aOR: 1.58; 95%CI, 1.50-1.67). Younger (18-25 years) and older maternal age (36-45 years), those with public drug insurance, women with heart diseases, anxiety, and other psychiatric disorders in the year prior to pregnancy as well as having a history of depression or postpartum depression in the 10 years prior to pregnancy were associated with an increased risk of postpartum depression in the year following delivery. Moreover, maternal asthma was also associated with postpartum depression at 1 month (aOR: 1.32; 95%CI, 1.15-1.52) (Table 9). In the multivariate models, the same variables that were associated with an increased risk of postpartum depression in the year following delivery, and

being an urban resident, were found to be statistically associated with the risk of postpartum depression at 1 month. An exception was that both maternal age and the presence of heart diseases were not associated with the risk of postpartum depression at 1 month.

Consistent findings were found in the association between asthma during pregnancy and postpartum depression in the 3 months following delivery (aOR: 1.46; 95%CI, 1.33-1.60) (Table 10). Similarly, in the multivariate model, consistent associations in the risk of postpartum depression in the 3 months following delivery were found with the same variables that were statistically associated with the risk of postpartum depression at 1 year. Only women who delivered in spring had lower odds of postpartum depression 3 months following delivery.

Finally, the analyses stratified by the presence of depression or postpartum depression in the 10 years prior to pregnancy and during pregnancy revealed significant associations between maternal asthma and postpartum depression in all strata, regardless of the period of time in which we assessed the outcome (Table 11). We found that the risk of developing postpartum depression was larger among women with asthma than those without asthma, with the largest association at 1 year postpartum. Of note, we observed higher odds ratios of postpartum depression among women without depression or postpartum depression as compared to those with depression or postpartum depression in the 10 years before pregnancy. Among these women, the odds of postpartum depression increased gradually as the postpartum time period increased with much higher risks of developing depression at 12 months' postpartum (Table 11).

A GEE model including an interaction term between maternal asthma and postpartum depression confirmed that history of depression or postpartum depression in the 10 years before pregnancy significantly modified the association between asthma and postpartum depression, regardless of the period in which the outcome was assessed (p-value of the interaction term <0.0001; see Table 12).

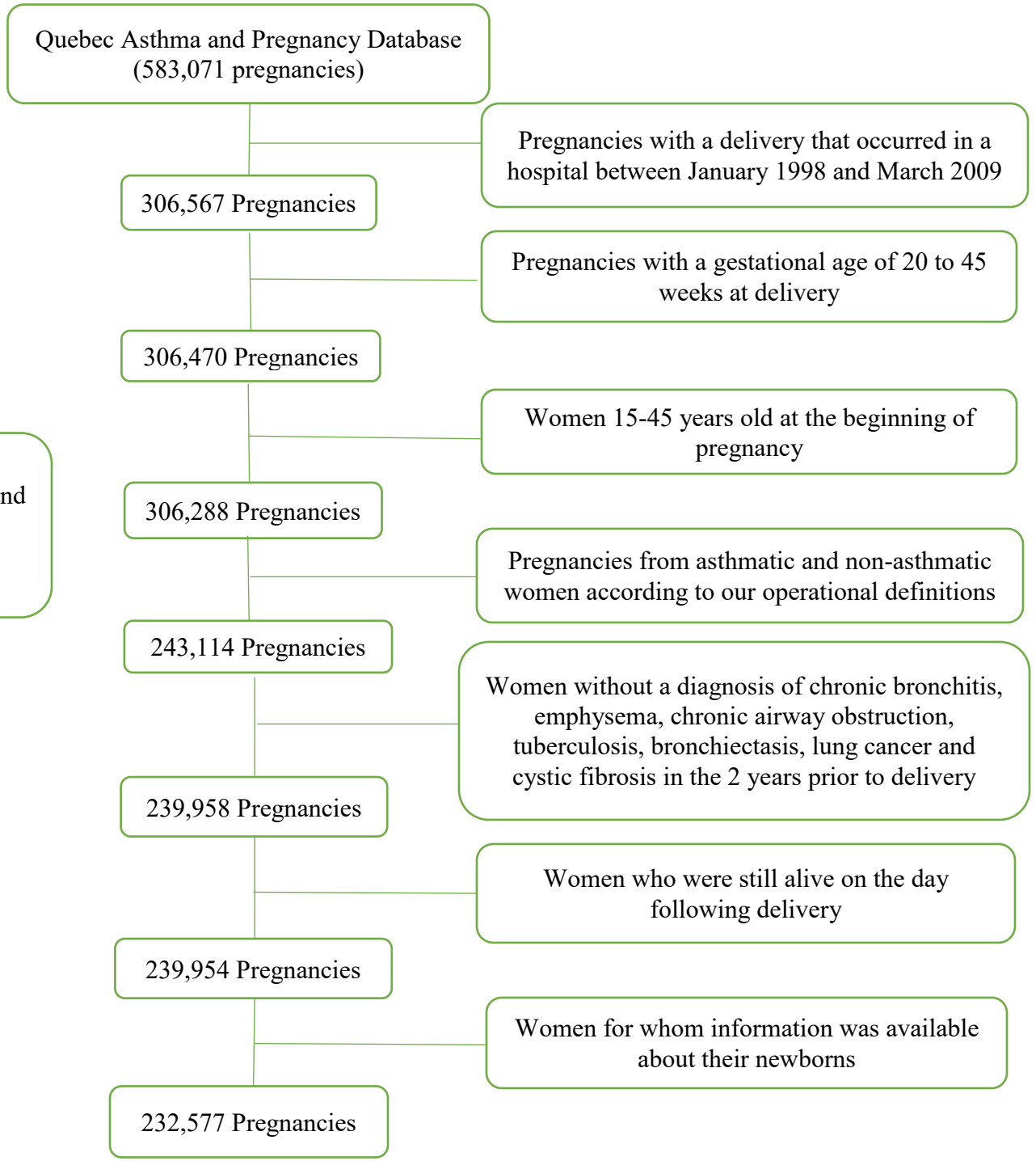


Figure 2. Cohort flow diagram and selection process.

Table 5. Characteristics of pregnancies of women with and without asthma

	Pregnancies of women with asthma (n=35,520)	Pregnancies of women without asthma (n=197,057)
	n (%)	n (%)
At the beginning of pregnancy		
Maternal age in years		
<18	957 (2.7)	2,701 (1.4)
18-25	12,974 (36.5)	56,883 (28.8)
26-35	19,095 (53.8)	120,327(61.1)
36-45	2,494 (7.0)	17,146 (8.7)
Urban residential area	29,792 (83.9)	161,219 (81.8)
Drug Insurance type		
Public with social welfare	5,562 (15.7)	15,888 (8.1)
Public without social welfare	8,142 (22.9)	43,786 (22.2)
Private	21,816 (61.4)	137,383 (69.7)
In the year prior to the current pregnancy		
Heart disease	532 (1.5)	1,505 (0.8)
Epilepsy	177 (0.5)	484 (0.3)
Diabetes mellitus	580 (1.6)	2,079 (1.1)
Anxiety	3,248 (9.1)	10,086 (5.1)
Other psychiatric disorders*	697 (2.0)	1,156 (0.6)
In 10 years prior to the current pregnancy		
Previous miscarriage	8,528 (24.0)	38,816 (19.7)
History of depression or postpartum depression	5,449 (15.3)	14,472 (7.3)
At least 1 delivery	8,428 (23.7)	65,442 (33.2)
Maternal characteristics during pregnancy		
Depression	950 (2.7)	2401 (1.2)

Anxiety	1,796 (5.1)	5,630 (2.9)
Anaemia	959 (2.7)	4,012 (2.0)
Gestational diabetes	2,678 (7.5)	10,618 (5.4)
Pre-eclampsia	1,165 (3.3)	4,489 (2.3)
Hyperemesis gravidarum	465 (1.3)	1,377 (0.7)
Delivery characteristics		
Preterm birth (<37 weeks of gestation)	3,269 (9.2)	13,711 (7.0)
Mode of delivery during current pregnancy		
Caesarean delivery	5,977 (16.8)	28,154 (14.3)
Vaginal delivery	20,837 (58.7)	121,396 (61.6)
Unknown	8,706 (24.5)	47,507 (24.1)
Season of delivery		
Winter	8,960 (25.2)	49,400 (25.1)
Spring	8,967 (25.2)	50,815 (25.8)
Summer	9,009 (25.4)	50,510 (25.6)
Autumn	8,584 (24.2)	46,332 (23.5)
Fetal / Infant characteristics		
Low birth weight ≤2500g	2,415 (6.8)	9,248(4.7)
Poor fetal growth during pregnancy**	1,028 (2.9)	4,183 (2.1)
Stillbirth (fetal loss ≥20 weeks of gestation)	150 (0.4)	773 (0.4)
Any congenital malformation at delivery	3,716 (10.5)	18,722 (9.5)

* Psychiatric disorders include schizophrenia, bipolar, psychotic and personality disorders.

** Poor fetal growth during pregnancy identified by using diagnostic codes (ICD-9: 656.5 and ICD-10: O36.5).

Table 6. Characteristics of pregnancies of women with and without asthma stratified by the presence or absence of history of depression or postpartum depression in 10 years prior to the current pregnancy

	History of depression or postpartum depression 10 years prior to current pregnancy (n=19,921)		No history of depression or postpartum depression 10 years prior to current pregnancy (n=212,656)	
	Pregnancies of women with asthma (n=5,449)	Pregnancies of women without asthma (n=14,472)	Pregnancies of women with asthma (n=30,071)	Pregnancies of women without asthma (n=182,585)
	n (%)	n (%)	n (%)	n (%)
At the beginning of pregnancy				
Maternal age in years				
<18	153 (2.8)	186 (1.3)	804 (2.7)	2,515 (1.4)
18-25	1,973 (36.2)	3,955 (27.3)	11,001 (36.6)	52,928 (29.0)
26-35	2,852 (52.3)	8,752 (60.5)	16,243 (54.0)	111,575 (61.1)
36-45	471 (8.7)	1,579 (10.9)	2,023 (6.7)	15,567 (8.5)
Urban residential area	4,580 (84.1)	11,863 (82.0)	25,212 (83.8)	149,356 (81.8)
Drug Insurance type				
Public with social welfare	1,393 (25.5)	1,810 (12.5)	4,169 (13.9)	14,078 (7.7)
Public without social welfare	1,214 (22.3)	3,170 (22.0)	6,928 (23.0)	40,616 (22.2)
Private	2,842 (52.2)	9,492 (65.5)	18,974 (63.1)	12,7891 (70.1)
In the year prior to the current pregnancy				
Heart disease	112 (2.1)	190 (1.3)	420 (1.4)	1,315 (0.7)
Epilepsy	48 (0.9)	59 (0.4)	129 (0.4)	425 (0.2)
Diabetes mellitus	130 (2.4)	182 (1.3)	450 (1.5)	1,897 (1.0)
Anxiety	1,278 (23.5)	2,782 (19.2)	1,970 (6.6)	7,304 (4.0)
Other psychiatric disorders*	508 (9.3)	714 (5.0)	189 (0.6)	442 (0.2)
In 10 years prior to the current pregnancy				
Previous miscarriage	1,590 (29.2)	3,726 (25.8)	6,938 (23.1)	35,090 (19.2)
At least 1 delivery	1,346 (24.7)	4,978 (34.4)	7,082 (23.6)	60,464 (33.1)

Maternal characteristics during pregnancy				
Depression	595 (11.0)	1,296 (9.0)	355 (1.2)	1,105 (0.6)
Anxiety	649 (12.0)	1,227 (8.5)	1,147 (3.8)	4,403 (2.4)
Anaemia	177 (3.3)	308 (2.1)	782 (2.6)	3,704 (2.0)
Gestational diabetes	520 (9.5)	925 (6.4)	2,158 (7.2)	9,693 (5.3)
Pre-eclampsia	215 (4.0)	351 (2.4)	950 (3.2)	4,138 (2.3)
Hyperemesis gravidarum	109 (2.0)	161 (1.1)	356 (1.2)	1,216 (0.7)
Delivery characteristics				
Preterm birth (<37 weeks of gestation)	632 (11.6)	1,222 (8.4)	2637 (8.8)	12,489 (6.8)
Mode of delivery during current pregnancy				
Caesarean delivery	983 (18.0)	2,219 (15.3)	4,994 (16.6)	25,935 (14.2)
Vaginal delivery	3,082 (56.6)	8,616 (59.6)	17,755 (59.0)	112,780 (61.8)
Unknown	1,384 (25.4)	3,637 (25.1)	7,322 (24.4)	43,870 (24.0)
Season of delivery				
Winter	1,353 (24.8)	3,541 (24.5)	7,607 (25.3)	45,859 (25.1)
Autumn	1,367 (25.1)	3,465 (23.9)	7,217 (24.0)	42,867 (23.5)
Spring	1,360 (25.0)	3,744 (25.9)	7,607 (25.3)	47,071 (25.8)
Summer	1,369 (25.1)	3,722 (25.7)	7,640 (25.4)	46,788 (25.6)
Fetal / infant characteristics				
Low birth weight ≤2500g	465 (8.5)	859 (5.9)	1,950 (6.5)	8,389 (4.6)
Poor fetal growth during pregnancy	191 (3.5)	314 (2.2)	837 (2.8)	3,869 (2.1)
Stillbirth (fetal loss ≥20 weeks of gestation)	28 (0.5)	64 (0.4)	122 (0.4)	709 (0.4)
Any congenital malformation at delivery	592 (10.9)	1,424 (9.8)	3,124 (10.4)	17,298 (9.5)

* Psychiatric disorders include schizophrenia, bipolar, psychotic and personality disorders.
** Poor fetal growth during pregnancy identified by using diagnostic codes (ICD-9: 656.5 and ICD-10: O36.5).

Table 7. Proportions of women with postpartum depression at 1 month, 3 months and 1 year postpartum among women with and without asthma during pregnancy

	1 month postpartum	3 months postpartum	1 year postpartum
	n (%)	n (%)	n (%)
Women with asthma during pregnancy (n= 35,520)	297 (0.8)	721 (2.0)	2,150 (6.1)
Women without asthma during pregnancy (n= 197,057)	839 (0.4)	1,917 (1.0)	5,738 (2.9)

Table 8. Crude and adjusted odds ratios (OR) of postpartum depression associated with asthma during pregnancy in the year following delivery

	Number of pregnancies	Number of cases of postpartum depression (%)	Crude OR (95% CI)	Adjusted OR (95% CI) *
Asthma during pregnancy				
Yes	35,520	2,150 (6.1)	2.12 (2.01-2.24)	1.58 (1.50-1.67)
No	197,057	5,738 (2.9)	(reference)	(reference)
At the beginning of pregnancy				
Maternal age in years				
<18	3,658	163 (4.5)	1.41 (1.20-1.65)	1.19 (1.00-1.41)
18-25	69,857	2,598 (3.7)	1.18 (1.12-1.24)	1.08 (1.03-1.14)
26-35	139,422	4,379 (3.1)	(reference)	(reference)
36-45	19,640	748 (3.8)	1.21 (1.11-1.30)	1.12 (1.03-1.22)
Residential area				
Urban	191,011	6,519 (3.4)	1.03 (0.97-1.09)	1.00 (0.94-1.07)
rural	41,566	1,369 (3.3)	(reference)	(reference)
Drug Insurance type				
Public with social welfare	21,450	1,288 (6.0)	2.03 (1.90-2.17)	1.42 (1.32-1.52)
Public without social welfare	51,928	1,844 (3.6)	1.19 (1.13-1.26)	1.13 (1.07-1.19)
Private	159,199	4,756 (3.0)	(reference)	(reference)
In the year prior to the current pregnancy				
Heart disease				
Yes	2,037	134 (6.6)	2.00 (1.68-2.38)	1.39 (1.15-1.69)
No	230,540	7,754 (3.4)	(reference)	(reference)
Epilepsy				
Yes	661	48 (7.3)	2.17 (1.60-2.95)	1.31 (0.95-1.82)
No	231,916	7,840 (3.4)	(reference)	(reference)
Diabetes mellitus				
Yes	2,659	110 (4.1)	1.21 (1.00-1.47)	1.01 (0.82-1.23)

No	229,918	7,778 (3.4)	(reference)	(reference)
Anxiety				
Yes	13,334	1,385 (10.4)	3.55 (3.33-3.78)	2.06 (1.92-2.20)
No	219,243	6,503 (3.0)	(reference)	(reference)
Other psychiatric disorders*				
Yes	1,853	421 (22.7)	7.86 (6.98-8.85)	2.24 (1.97-2.54)
No	230,724	7,467 (3.2)	(reference)	(reference)
In 10 years prior to pregnancy				
Previous miscarriage				
Yes	47,344	1,858 (3.9)	1.20 (1.14-1.27)	1.03 (0.98-1.09)
No	185,233	6,030 (3.3)	(reference)	(reference)
History of depression or postpartum depression				
Yes	19921	2699 (13.6)	6.04 (5.74-6.36)	4.43 (4.18-4.69)
No	212656	5189 (2.4)	(reference)	(reference)
At least 1 delivery				
Yes	73,870	2,333 (3.2)	0.94 (0.89-0.98)	0.95 (0.90-1.00)
No	158,707	5,555 (3.5)	(reference)	(reference)
Delivery characteristics				
Season of delivery				
Winter	58,360	1,940 (3.3)	0.98 (0.92-1.04)	0.97 (0.91-1.04)
Autumn	54,916	1,915 (3.5)	1.02 (0.96-1.09)	1.01 (0.95-1.08)
Spring	59,782	2,008 (3.4)	0.99 (0.93-1.05)	0.99 (0.93-1.05)
Summer	59,519	2,025 (3.4)	(reference)	(reference)

*Adjusted for maternal age, the area of residence, drug insurance status, anxiety, diabetes mellitus, epilepsy, heart diseases in the year prior to the current pregnancy, previous miscarriage, depression or postpartum depression, at 1 least 1 delivery in the 10 years prior to the current pregnancy and season of delivery.

Table 9. Crude and adjusted odds ratios (OR) of postpartum depression associated with asthma during pregnancy in the 1 month following delivery

	Number of pregnancies	Number of cases of postpartum depression (%)	Crude OR (95% CI)	Adjusted OR (95% CI) *
Asthma during pregnancy				
Yes	35520	297 (0.8)	1.95 (1.71-2.23)	1.32 (1.15-1.52)
No	197057	839 (0.4)	(reference)	(reference)
At the beginning of pregnancy				
Maternal age in years				
<18	3658	13 (0.4)	0.72 (0.41-1.24)	0.57 (0.32-0.99)
18-25	69857	308 (0.4)	0.89 (0.78-1.02)	0.80 (0.69-0.92)
26-35	139422	688 (0.5)	(reference)	(reference)
36-45	19640	127 (0.7)	1.30 (1.08-1.58)	1.17 (0.97-1.42)
Residential area				
Urban	191011	976 (0.5)	1.31 (1.10-1.56)	1.24 (1.04-1.47)
rural	41566	160 (0.4)	(reference)	(reference)
Drug Insurance type				
Public with social welfare	21450	197 (0.9)	2.17 (1.84-2.55)	1.43 (1.19-1.70)
Public without social welfare	51928	260 (0.5)	1.18 (1.02-1.36)	1.15 (0.99-1.33)
Private	159199	679 (0.4)	(reference)	(reference)
In the year prior to the current pregnancy				
Heart disease				
Yes	2037	19 (0.9)	1.94 (1.24-3.04)	1.17 (0.72-1.88)
No	230540	1117 (0.5)	(reference)	(reference)
Epilepsy				
Yes	661	7 (1.1)	2.19 (1.04-4.63)	1.07 (0.49-2.32)
No	231916	1129 (0.5)	(reference)	(reference)
Diabetes mellitus				
Yes	2659	18 (0.7)	1.35 (0.84-2.17)	1.09 (0.68-1.76)
No	229918	1118 (0.5)	(reference)	(reference)

Anxiety				
Yes	13334	245 (1.8)	4.42 (3.82-5.12)	2.07 (1.75-2.45)
No	219243	891 (0.4)	(reference)	(reference)
Other psychiatric disorders*				
Yes	1853	110 (5.9)	13.35 (10.80-16.51)	3.33 (2.62-4.23)
No	230724	1026 (0.4)	(reference)	(reference)
In 10 years prior to pregnancy				
Previous miscarriage				
Yes	47344	250 (0.5)	1.09 (0.94-1.26)	0.91 (0.79-1.06)
No	185233	886 (0.5)	(reference)	(reference)
History of depression or postpartum depression				
Yes	19921	474 (2.4)	7.58 (6.71-8.57)	5.21 (4.50-6.02)
No	212656	662 (0.3)	(reference)	(reference)
At least 1 delivery				
Yes	73870	315 (0.4)	0.84 (0.74-0.95)	0.84 (0.73-0.96)
No	158707	821 (0.5)	(reference)	(reference)
Delivery characteristics				
Season of delivery				
Winter	58360	269 (0.5)	0.86 (0.73-1.01)	0.86 (0.73-1.01)
Autumn	54916	264 (0.5)	0.89 (0.76-1.05)	0.88 (0.75-1.04)
Spring	59782	284 (0.5)	0.89 (0.76-1.04)	0.88 (0.75-1.04)
Summer	59519	319 (0.5)	(reference)	(reference)

*Adjusted for maternal age, the area of residence, drug insurance status, anxiety, diabetes mellitus, epilepsy, heart diseases in the year prior to the current pregnancy, previous miscarriage, depression or postpartum depression, at 1 least 1 delivery in the 10 years prior to the current pregnancy and season of delivery.

Table 10. Crude and adjusted odds ratios (OR) of postpartum depression associated with asthma during pregnancy in the 3 months following delivery

	Number of pregnancies	Number of cases of postpartum depression (%)	Crude OR (95% CI)	Adjusted OR (95% CI) *
Asthma during pregnancy				
Yes	35520	721 (2.0)	2.09 (1.91-2.28)	1.46 (1.33-1.60)
No	197057	1917 (1.0)	(reference)	(reference)
At the beginning of pregnancy				
Maternal age in years				
<18	3658	42 (1.2)	1.04 (0.76-1.42)	0.84 (0.61-1.16)
18-25	69857	792 (1.1)	1.03 (0.94-1.12)	0.93 (0.85-1.02)
26-35	139422	1526 (1.1)	(reference)	(reference)
36-45	19640	278 (1.4)	1.28 (1.13-1.46)	1.17 (1.03-1.34)
Residential area				
Urban	191011	2223 (1.2)	1.15 (1.04-1.28)	1.11 (0.99-1.24)
rural	41566	415 (1.0)	(reference)	(reference)
Drug Insurance type				
Public with social welfare	21450	456 (2.1)	2.17 (1.95-2.42)	1.45 (1.29-1.64)
Public without social welfare	51928	623 (1.2)	1.23 (1.12-1.35)	1.18 (1.07-1.30)
Private	159199	1559 (1.0)	(reference)	(reference)
In the year prior to the current pregnancy				
Heart disease				
Yes	2037	41 (2.0)	1.79 (1.32-2.44)	1.13 (0.82-1.57)
No	230540	2597 (1.1)	(reference)	(reference)
Epilepsy				
Yes	661	17 (2.6)	2.30 (1.40-3.76)	1.23 (0.73-2.06)
No	231916	2621 (1.1)	(reference)	(reference)
Diabetes mellitus				
Yes	2659	37 (1.4)	1.19 (0.85-1.66)	0.95 (0.68-1.34)
No	229918	2601 (1.1)	(reference)	(reference)

Anxiety				
Yes	13334	541 (4.1)	4.17 (3.78-4.61)	2.1 (1.88-2.35)
No	219243	2097 (1.0)	(reference)	(reference)
Other psychiatric disorders*				
Yes	1853	199 (10.7)	10.44 (8.90-12.24)	2.58 (2.16-3.08)
No	230724	2439 (1.1)	(reference)	(reference)
In 10 years prior to pregnancy				
Previous miscarriage				
Yes	47344	586 (1.2)	1.10 (1.01-1.21)	0.92 (0.84-1.01)
No	185233	2052 (1.1)	(reference)	(reference)
History of depression or postpartum depression				
Yes	19921	1066 (5.4)	7.31 (6.74-7.93)	5.19 (4.72-5.71)
No	212656	1572 (0.7)	(reference)	(reference)
At least 1 delivery				
Yes	73870	776 (1.1)	0.92 (0.85-0.99)	0.93 (0.85-1.01)
No	158707	1862 (1.2)	(reference)	(reference)
Delivery characteristics				
Season of delivery				
Winter	58360	644 (1.1)	0.91 (0.82-1.01)	0.90 (0.81-1.01)
Autumn	54916	621 (1.1)	0.92 (0.83-1.03)	0.91 (0.82-1.02)
Spring	59782	648 (1.1)	0.89 (0.80-0.99)	0.89 (0.79-0.99)
Summer	59519	725 (1.2)	(reference)	(reference)

*Adjusted for maternal age, the area of residence, drug insurance status, anxiety, diabetes mellitus, epilepsy, heart diseases in the year prior to the current pregnancy, previous miscarriage, depression or postpartum depression, at 1 least 1 delivery in the 10 years prior to the current pregnancy and season of delivery.

Table 11. Adjusted odds ratios for the association between asthma during pregnancy and postpartum depression at 1 month, 3 months and 1 year postpartum in the entire cohort and stratified by the presence or absence of depression or postpartum depression 10 years prior to the current pregnancy

	Number of pregnancies	**Number of cases of postpartum depression (%)**	**Adjusted OR (95% CI) ***
Entire cohort (n=232,577)			
1 month postpartum	35,520 197,057	297 (0.8) 839 (0.4)	1.32 (1.15-1.52) (reference)
3 months postpartum	35,520 19,7057	721 (2.0) 1,917 (1.0)	1.46 (1.33-1.60) (reference)
1 year postpartum	35,520 197,057	2,150 (6.1) 5,738 (2.9)	1.58 (1.50-1.67) (reference)
Women with depression or postpartum depression 10 years prior to the current pregnancy (n=19,921)			
1 month postpartum	5,449 14,472	162 (3.0) 312 (2.2)	1.30 (1.06-1.59) (reference)
3 months postpartum	5,449 14,472	364 (6.7) 702 (4.9)	1.30 (1.13-1.49) (reference)
1 year postpartum	5,449 14,472	908 (16.7) 1791 (12.4)	1.29 (1.18-1.42) (reference)
Women without depression or postpartum depression 10 years prior to the current pregnancy (n=212,656)			
1 month postpartum	30,071 182,585	135 (0.5) 527 (0.3)	1.35 (1.12-1.64) (reference)
3 months postpartum	30,071 182,585	357 (1.2) 1,215 (0.7)	1.60 (1.41-1.80) (reference)
1 year postpartum	30,071 182,585	1,242 (4.1) 3,947 (2.1)	1.75 (1.64-1.87) (reference)
Women without depression or postpartum depression 10 years prior to pregnancy and without depression during pregnancy (n=211,196)			
1 month postpartum	29,716 181,480	106 (0.4) 435 (0.2)	1.30 (1.05-1.61) (reference)
3 months postpartum	29,716 181,480	308 (1.0) 1,076 (0.6)	1.57 (1.38-1.79) (reference)
1 year postpartum	29,716 181,480	1,158 (3.9) 3,712 (2.1)	1.75 (1.63-1.87) (reference)

*Adjusted for maternal age, the area of residence, drug insurance status, anxiety, diabetes mellitus, epilepsy, heart diseases in the year prior to the current pregnancy, previous miscarriage, depression or postpartum depression, at 1 least 1 delivery in the 10 years prior to the current pregnancy and season of delivery.

Table 12. The GEE interaction model of the association between maternal asthma and postpartum depression (at 1 month, 3 months and 1 year postpartum)

	Adjusted OR (95% CI) [a]
1 month postpartum	
Asthma during pregnancy Yes No	 1.55 (1.28-1.87) (reference)
Depression or postpartum depression 10 years prior to the current pregnancy Yes No	 7.35 (6.35-8.5) (reference)
Asthma during pregnancy*depression or postpartum depression 10 years prior to the current pregnancy Yes No	 1.41 (1.21-1.61) (reference)
3 months postpartum	
Asthma during pregnancy Yes No	 1.78 (1.58-2.01) (reference)
Depression or postpartum depression 10 years prior to the current pregnancy Yes No	 7.27 (6.59-8.02) (reference)
Asthma during pregnancy*depression or postpartum depression 10 years prior to the current pregnancy Yes No	 1.42 (1.28-1.56) (reference)
1 year postpartum	
Asthma during pregnancy Yes No	 1.94 (1.82-2.07) (reference)
Depression or postpartum depression 10 years prior to the current pregnancy Yes No	 6.11 (5.74-6.50) (reference)
Asthma during pregnancy*depression or postpartum depression 10 years prior to the current pregnancy Yes No	 1.45 (1.36-1.54) (reference)

[a] The model includes an interaction term between maternal asthma during pregnancy and women with a history of depression or postpartum depression in the 10 years prior to the current pregnancy.

CHAPTER 6: DISCUSSION

Discussion

This chapter presents a discussion of the results included in the thesis. In addition, this section will illustrate the contribution of the results in the field of asthma during pregnancy and postpartum depression. Finally, we will present the strength and weakness of the study.

6.1 General discussion

Asthma is one of the most prevalent chronic diseases encountered during pregnancy (1-3). The disease affects about 3.4% to 12.4% of pregnant women and shows an increasing prevalence over time (2-6). In the United States, trends in asthma prevalence have been increased over the past several decades, particularly among younger age groups. These trends suggest a concurrent increase in the prevalence of asthma among pregnant women (44, 45). Several studies have revealed that adverse pregnancy outcomes were higher among asthmatic women than non-asthmatic women, including preeclampsia, antepartum hemorrhage, hypertensive disorders of pregnancy, caesarean delivery, placenta previa, and postpartum bleeding (2, 3, 7).

Postpartum depression is a nonpsychotic depressive episode starting in the postpartum period (58, 59). At present, postpartum depression is not classified as a separate disease; it is diagnosed as part of affective or mood disorders in both DSM-IV (American Psychiatric Association, 1994) and ICD10 (World Health Organization, 1993). According to the DSM-IV, postpartum depression is a depressive disorder with onset within the first 4 weeks after delivery. Postpartum depression (PPD) is a serious and debilitating illness that affects approximately 10%-15% worldwide (8-10). In Canada, there are studies showed that the prevalence of postpartum depression increased from 8.7% to 16.4% from 2011 to 2014 (60, 61). Symptoms of postpartum depression include anxiety, guilt, negative maternal attitudes, and poor parenting

self-efficacy (136, 137). The period in which postpartum depression was measured differs considerably between studies (8, 18, 19). These episodes start after delivery and may last one year postpartum (17). Most studies in the literature assessed postpartum depression at 1 month and 3 months after childbirth (20-22). However, according to Canadian guidelines 'Nursing Best Practice Guidelines' in 2005, they stated that the onset of postpartum depression occurs within 1 year postpartum (23).

There is also evidence from several epidemiological studies on the increased risk of depression among women with asthma outside of pregnancy, with effect size ranging between 1.4 and 2.8 (27-29). This study was the first specifically designed to investigate the association between asthma during pregnancy and postpartum depression. The purpose of this study was to compare the risk of postpartum depression at three different time periods (at 1 month, 3 months and 1 year postpartum) between pregnant women with and without asthma.

6.2 Contribution of our results to the literature in the field of asthma during pregnancy and postpartum depression

This is the first study to assess the impact of maternal asthma and postpartum depression as a primary outcome. Maternal asthma was associated with an increased risk of developing postpartum depression in the three periods assessed; 32% at 1 month, 46% at 3 months and 58% at 1 year postpartum. Based on our results asthma during pregnancy is considered as a risk factor of postpartum depression. Although these results supported our research hypothesis in a representative population-based cohort, future studies are warranted to confirm findings from our study. Our results also showed that this association was present in women with and without

depression or postpartum depression in the 10 years before pregnancy and also among those women without depression during pregnancy. However, the association was stronger among those without previous depression or postpartum depression in the 10 years before pregnancy. According to the Canadian network for mood and anxiety treatment (CANMAT) clinical guidelines, the maximum benefit for taking the antidepressant appear at 6 to 9 months after the initiation of therapy (138). Therefore, our findings could be explained by the fact that the subgroup of women with depression or postpartum depression prior to pregnancy might have been more likely to be treated with antidepressant medications before or during pregnancy. This is only a hypothesis and further studies are needed to confirm whether it is true or not.

To the best of our knowledge, this is the first study specifically designed to examine the association between asthma during pregnancy and postpartum depression. However, we found one previous case-control study based on Taiwanese administrative databases that reported data on this association, but this study was designed to assess the impact of the mode and season of delivery on postpartum depression, and maternal asthma was only considered as a potential confounder (32). The study which included 2,107 cases of postpartum depression and 8,428 controls selected between 2003 and 2006 showed that asthma during pregnancy was associated with an increased risk of postpartum depression within the first 6 months following delivery, but this association did not reach statistical significance (OR: 1.3; 95% CI, 0.98, 1.73) (32). However, some limitations should be taken into account in the interpretation of the results of this study. It was based on health administrative databases that did not include information about possible risk factors of PPD, such as the lack of social support, family income, education of the mother, area of residence and diabetes mellitus. Not controlling for those variables might have

resulted in residual confounding and possibly lead to overestimation of the association between asthma during pregnancy and postpartum depression as they are found more prevalent among women with asthma compared to women without asthma (139-143). Meanwhile, because of the fact that maternal asthma was not the exposure of interest, the association was adjusted for variables that might be in the causal pathway between maternal asthma and postpartum depression, including antepartum depression, early onset of delivery, and poor fetal growth. Such adjustment could have biased the estimate of the association between asthma during pregnancy and PPD towards the null.

Several epidemiological studies have reported an association between asthma and depression outside of pregnancy (27, 29, 66, 68). The biological mechanisms explaining the link between asthma and depression are still unclear, but several hypotheses exist and could possibly explain the association between asthma during pregnancy and postpartum depression. The first hypothesis is related to stress and glucocorticoid resistance. Indeed, the experience of significant stress early in life is considered as a risk factor for the development of both depression and asthma and, via glucocorticoid resistance, may represent the most significant link between the two conditions (31). A subset of patients who are exposed to psychological/emotional stress early in life has delicate dysregulation of the sympathetic and parasympathetic nervous systems and the hypothalamic-pituitary-adrenal axis, including glucocorticoid resistance, which biases the immune system toward a T helper 2 (Th2) response (31, 144), immune system hyperactivity and inflammation. It is possible that increased inflammation brings out a latent genetic risk for both asthma and depression, with the former having either a lower threshold for expression or with developmental factors interacting with inflammation to produce asthma. Suffering from a

stressful experience may cause the developing autonomic nervous system to be more labile, which can change into emotionally triggered asthma symptoms (145). Glucocorticoids suppress asthma symptoms successfully in most of patients; however, a small number of patients fails to respond to exogenous steroids, even when they are taken high doses (146). These patients usually had asthma longer than the average patients and manifest irreversible airflow obstruction and a greater inflammatory burden (147). Glucocorticoids signaling defects are also existing in depressed patients (148). About 50% of the persons who suffer from depression have higher levels of cortisol and corticotropin-releasing hormone (149, 150), with very high rates of dexamethasone non-suppression (151). The second hypothesis is the role of cytokines. Cytokines affect inflammatory responses, and the processes they govern are implicated in the pathophysiology of many diseases, including those with central nervous system manifestations (30). Peripheral cytokines can cause an increase in the glial cell release of cytokine of the brain via the vagus and glossopharyngeal nerves rather than acting directly on the brain themselves (152). The intersection of the cytokine and hypothalamic-pituitary-adrenal systems is mechanistically relevant to the development of both asthma and depression. Depression is characterized by immune activation, mainly the innate immune system (26). Sickness behaviour, the emotional and behavioural symptoms that develop as a consequence of acute infection or cytokine therapy, appears to be the result of augmented levels of the pro-inflammatory cytokines interleukin (IL)-1 and tumour necrosis factor (TNF) and is the most commonly cited evidence linking cytokine activation with depression. When individuals are exposed to an allergen or irritant, an imbalance between T helper 1 (Th1) and T helper 2 (Th2) cells occurs and certain types of inflammatory cells (e.g., mast cells) are activated (153). This consequently results in an over-expression of Th2 related cytokines and reduction of Th1 related

cytokines that are linked to asthma development. There are also documented evidence on the effects of depression on memory, attention, sleep, alteration of appetite and decision-making (154-157). All of these cognitive mechanisms are involved in patient compliance with treatment, and are therefore related to self-management plans and expected management outcomes (158). Serious deficiencies in making decisions to seek medical help or call an ambulance have been reported in cases of a slow-onset asthma attack (159).

6.3 Strengths of the study

6.3.1 Databases

One of the strengths of our study is the use of prospectively gathered data from administrative databases. Using the interlinked two large Quebec's databases to identify the exposures and outcomes provided many advantages over other methods of data collection such as a self-reported questionnaire or a personal interview (127-129).

First, data on asthma diagnosis were prospectively collected and independently of the outcome, thus excluding the possibility of recall bias. *Second*, using administrative databases, we had the ability to study a large number of pregnant women in a reasonable budget and time-frame. *Third*, data recorded in the medical diagnosis of asthma recorded in the RAMQ Medical Services database has been formally evaluated and found to be valid and precise (160, 161). The RAMQ and MED-ECHO databases have often been used for research on asthma and pregnancy with many articles published in renowned medical journals (162-165).

Pregnancy variables recorded in the RAMQ and MED-ECHO databases have been formally evaluated and found to be highly valid (122). From the variables that have been validated and were used to perform our analyses are maternal age, the length of gestation, date of delivery, and date of last menstruation. The validity of the variables was assessed by calculating Pearson correlation coefficient between the values obtained from the databases and patients' medical charts, and the correlations were found to be high for all variables ranging from 0.920 to 0.999. In addition, the validity of the operational definition of asthma was validated using Ontarian administrative databases (123).

6.3.2 External validity

External validity generally refers to which extent a study's findings could be applied to other non-study populations (generalizability) (127-129, 166). We did not consider using the medications for asthma or depression in our analysis as we did not have information on pharmaceutical services of the private drug insurance which accounts for about 60% of the population of this study. On the other hand, 40% of the women that have public drug insurance might represent women with lower socio-economic status (welfare recipients, and employees who have no access to a drug plan from their employer or spouse's employer) and they are alone not representative of the study population. Therefore, we decided to include all pregnancies from women with asthma and all pregnancies from a random sample of women without asthma selected between January 1, 1990, and March 31, 2010. These pregnancies were identified from the delivery hospitalization record in the MED-ECHO database, independently of the drug insurance plan. This decision was taken to ensure the representativeness of the study population. In addition, we assessed three different time periods for postpartum depression (1 month, 3

months, and 1 year postpartum), as there was no consensus in the literature on the most appropriate period to assess postpartum depression. Thus, this study will add new insights into the possible link between asthma during pregnancy and postpartum depression in pregnant women.

6.4 Limits of the study

Two types of error could alter study results; random error and systematic error (bias) (127-129).

6.4.1 Random error

Random error (chance effect) is defined as the variability in the data and it represents the precision of the estimate. Random error usually diminishes as the sample size gets large. A small P-value and a narrow confidence interval are reassuring signs against chance effect (127-129). As mentioned earlier, we had a large cohort that included 232,577 pregnancies (35,520 from women with asthma and 197,057 from women without asthmatic) that reached the 20^{th} week of gestation and delivered between January 1998 and March 2009. Therefore, the large sample size in the study would decrease the effect of the random error.

6.4.2 Systematic error

Systematic error in a research study leads to a difference between an observed value and the true value due to all causes other than sampling variability (167). It could occur due to errors in the way the subjects were selected, errors in the measurement of variables, or any confounding factor that is not completely controlled for. Systematic error mainly influences the internal validity of the study and bias can be classified into selection bias, information bias, and confounding bias (127-129). Selection bias refers to any error that arises in the process of

identifying the study populations, and in a cohort it is usually related to losses to follow-up (127-129). In our study, we don't believe that we faced a situation in which this kind of bias could have altered our results.

6.4.2.1 Information bias

Information bias occurs as a result of systematic differences in the way data on exposure, outcome, or confounders are obtained from the various study groups (127-129). Misclassification is the reason behind information bias, which can be differential or non-differential misclassification (127-129).

In retrospective cohort studies, in which information is obtained from past records, differential misclassification could be present if the quality and accuracy of information gathered are different among exposed and non-exposed persons (129). In our study, the assessment of the outcome (cases of postpartum depression) was identified using diagnostic codes recorded in the RAMQ and MED-ECHO databases (administrative databases) and was not specifically validated for this study, but the assessment of the outcome was made independently of the exposure. Consequently, if there was any inaccuracy in the outcome measurement, it will not be related to exposure status and only non-differential misclassification may have resulted. Non-differential misclassification generally dilutes the effect (towards null effect) and produces underestimation of the OR (127). Since there are no specific codes of postpartum depression in the literature, we decided to use the diagnostic codes of depression from the definition of Statistics Canada recorded in the RAMQ or MED-ECHO databases (125). Our list of codes was verified by a psychologist from the Hôpital du Sacré-Coeur de Montréal.

We decided to use these codes as they demonstrated the highest specificities with a greater likelihood that those who are not depressed will be identified more correctly than using other definitions in the literature (126). In addition, the fact that women with a chronic disease such as asthma may see more often physicians and seek medical attention to a greater extent than women without asthma might lead to postpartum depression diagnosed more frequently among women with asthma than among women without asthma. Consequently, this might lead to differential misclassification of the outcome and would bias the association away from the null. Further use of these diagnostic codes of postpartum depression in future studies are justified and will provide additional evidence on its validity among asthmatic pregnant women.

6.4.2.2 Confounding bias

Confounding is mixing of the effect of the exposure under study on the disease (outcome) with that of a third factor that is associated with the exposure, an independent risk factor for the disease, and not in the causal pathway between exposure and disease (even among individuals non-exposed to the exposure factor under study) (127-129). The consequence of confounding is that the estimated association is not the same as the true effect and an extraneous risk factor could be the alternative reason behind the association (or part of the association) observed between the exposure and the outcome (127-129). In order to reduce the impact of confounding in our study, we used generalized estimating equation (GEE) models to estimate the adjusted odds ratios (ORs) of postpartum while adjusting for several potential confounders. We included the majority of known risk factors of postpartum depression in our models, however, we were unable to adjust for a some well-known risk factors, like mother and husband education, unemployment, financial problems ,domestic violence, childhood physical abuse, lack of social

support by the partner and the family, poor marital relationship, family history of mental illness, weight gain during pregnancy, alcohol use during pregnancy, smoking during pregnancy, and unplanned pregnancy. We found evidence from the literature that poor marital relationship, family history of mental illness and alcohol use during pregnancy might have no difference in women with and without asthma (141, 168, 169) so; these variables will have no effect on the association between asthma during pregnancy and postpartum depression. However, findings from the literature suggest that mother/husband education, unemployment, financial problems, domestic violence, childhood physical abuse, lack of social support, weight gain during pregnancy, smoking during pregnancy and unplanned pregnancy are associated with increased risk of asthma (139-141, 170-175). Low education, unemployment, weight gain during pregnancy and smoking during pregnancy are more likely to have a strong positive association with both asthma and postpartum depression (24, 94, 113, 117, 139, 170, 173, 176), while financial problems, domestic violence, childhood physical abuse, lack of social support and unplanned pregnancy are associated with asthma and postpartum depression to a less extent (21, 24, 95, 96, 98, 100, 140, 141, 171, 172, 175). Therefore, we expect that not adjusting for these variables might possibly overestimate the association between maternal asthma and postpartum depression.

In addition, we did not adjust for mediators in our analysis such as 1) maternal characteristics during pregnancy (depression, anxiety, anemia, gestational diabetes, preeclampsia, hyperemesis gravidarum), 2) delivery characteristics (premature labor, preterm birth (< 37 weeks of gestation), mode of delivery), 3) maternal characteristics after delivery (subinvolution of uterus, urinary tract infection, difficulty of breastfeeding, postpartum anemia,

postpartum hemorrhage), 4) infant characteristics (low birth weight (≤2500g), poor fetal growth, ≥5 diarrheal episodes per year, perinatal death, stillbirth (fetal loss ≥20 weeks of gestation), temperamentally difficult child, inadequate baby care facilities after delivery, baby physical problems and congenital malformation at delivery) as it could have underestimated the association between asthma during pregnancy and postpartum depression.

CHAPTER 7: CONCLUSION AND PERSPECTIVES

Conclusion and perspective

The work presented in this thesis aimed at studying the association between asthma during pregnancy and postpartum depression. Briefly, our study showed an increase in the risk of developing postpartum depression among women with asthma compared to women without asthma in the three periods assessed, i.e. 1 month, 3 months and 1 year postpartum, with the highest association seen at 1 year postpartum (58% increase among women with asthma). Moreover, our results showed that this association was present in both subgroups of women with and without depression or postpartum depression before pregnancy, although significantly higher among women with no history of depression or postpartum depression.

Results of this thesis are relevant to physicians and other health care professionals who see pregnant asthmatic women every day in clinics and hospitals. In light of the aforementioned results, it would be recommended for physicians to monitor closely asthmatic pregnant women to detect the early signs of postpartum depression among these women more rapidly and intervene more efficiently, if necessary. Also, the prevention of postpartum depression among women with asthma could be attained with appropriate counseling measures during pregnancy. Therefore, it would be recommended to settle objectives for clinical management of asthma during pregnancy (39). These objectives include the prevention of chronic day and night symptoms, maintenance of optimal pulmonary function and normal activities, and prevention of exacerbations, using therapies with minimal or no adverse side-effects (39). In addition, it is important to maintain fetal oxygenation by preventing episodes of maternal hypoxia (39). Achieving these objectives require regular monitoring of clinical symptoms, provision of self-

management education and the correct use of pharmacotherapies. Moreover, there is some evidence showing that psychosocial or psychological intervention after childbirth helped reduce the risk of postpartum depression (177). Therefore, multidisciplinary management approach of all pregnant women with asthma by all health care professionals involved in a woman's care is encouraged (39).

The findings in our study could have an impact for future research. From one part, future studies from populations in other countries need to investigate the same association and accumulate evidence on the increased risk of postpartum depression among asthmatic women. In addition, studies that adjust for the confounders that were not measured in our administrative database are required to investigate the effect of these confounders on the association between asthma during pregnancy and postpartum depression. Moreover, future studies could aim at studying the effect of potential mediators that were listed in our study on the association between asthma during pregnancy and postpartum depression by using mediation analysis.

Reference List

1. Blais L, Beauchesne M- F, Rey É, Malo J- L, Forget A. Use of inhaled corticosteroids during the first trimester of pregnancy and the risk of congenital malformations among women with asthma. Thorax. 2007;62(4):320-8.

2. Demissie K, Breckenridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. American journal of respiratory and critical care medicine. 1998;158(4):1091-5.

3. Murphy VE, Gibson PG, Smith R, Clifton VL. Asthma during pregnancy: mechanisms and treatment implications. The European respiratory journal. 2005;25(4):731-50.

4. Alexander S, Dodds L, Armson BA. Perinatal outcomes in women with asthma during pregnancy. Obstetrics and gynecology. 1998;92(3):435-40.

5. Kwon HL, Belanger K, Bracken MB. Asthma prevalence among pregnant and childbearing-aged women in the United States: estimates from national health surveys. Annals of epidemiology. 2003;13(5):317-24.

6. Kurinczuk JJ, Parsons DE, Dawes V, Burton PR. The relationship between asthma and smoking during pregnancy. Women & health. 1999;29(3):31-47.

7. Schatz M. Interrelationships between asthma and pregnancy: a literature review. The Journal of allergy and clinical immunology. 1999;103(2 Pt 2):S330-6.

8. Alharbi AA, Abdulghani HM. Risk factors associated with postpartum depression in the Saudi population. Neuropsychiatr Dis Treat. 2014;10:311-6.

9. O'Hara M, Swain A. Rates and risk of postpartum depression – a meta-analysis. Int Rev Psychiatry. 1996;8(37):38-54.

10. Vigod SN, Villegas L, Dennis CL, Ross LE. Prevalence and risk factors for postpartum depression among women with preterm and low-birth-weight infants: a systematic review. BJOG : an international journal of obstetrics and gynaecology. 2010;117(5):540-50.

11. Beck CT. Teetering on the edge: a substantive theory of postpartum depression. Nursing research. 1993;42(1):42-8.

12. Robertson E, Grace S, Wallington T, Stewart DE. Antenatal risk factors for postpartum depression: a synthesis of recent literature. General hospital psychiatry. 2004;26(4):289-95.

13. Lyons-Ruth K, Zoll D, Connell D, Grunebaum HU. The depressed mother and her one-year-old infant: environment, interaction, attachment, and infant development. New directions for child development. 1986(34):61-82.

14. Murray L. The impact of postnatal depression on infant development. Journal of child psychology and psychiatry, and allied disciplines. 1992;33(3):543-61.

15. Stein A, Gath DH, Bucher J, Bond A, Day A, Cooper PJ. The relationship between post-natal depression and mother-child interaction. The British journal of psychiatry : the journal of mental science. 1991;158:46-52.

16. Murray L, Fiori-Cowley A, Hooper R, Cooper P. The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. Child development. 1996;67(5):2512-26.

17. American Psychological Association, Diagnostic and Statistical Manual of Mental Disorders. DSM-IV-TR, Text Revision. American Psychiatric Association, Washington, DC, USA. 2000(4th edition).

18. Chaudron LH. Postpartum depression: what pediatricians need to know. Pediatrics in review / American Academy of Pediatrics. 2003;24(5):154-61.

19. Boyce P, Hickey A. Psychosocial risk factors to major depression after childbirth. Social psychiatry and psychiatric epidemiology. 2005;40(8):605-12.

20. Davey HL, Tough SC, Adair CE, Benzies KM. Risk factors for sub-clinical and major postpartum depression among a community cohort of Canadian women. Maternal and child health journal. 2011;15(7):866-75.

21. Dennis CL, Vigod S. The relationship between postpartum depression, domestic violence, childhood violence, and substance use: epidemiologic study of a large community sample. Violence against women. 2013;19(4):503-17.

22. Sword W, Landy CK, Thabane L, Watt S, Krueger P, Farine D, et al. Is mode of delivery associated with postpartum depression at 6 weeks: a prospective cohort study. BJOG : an international journal of obstetrics and gynaecology. 2011;118(8):966-77.

23. Interventions for Postpartum Depression. Toronto, Canada: Registered Nurses' Association of Ontario (2005).

.

24. Inandi T, Elci OC, Ozturk A, Egri M, Polat A, Sahin TK. Risk factors for depression in postnatal first year, in eastern Turkey. International journal of epidemiology. 2002;31(6):1201-7.

25. Maes M. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. Progress in neuro-psychopharmacology & biological psychiatry. 2011;35(3):664-75.

26. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends in immunology. 2006;27(1):24-31.

27. Trojan TD, Khan DA, Defina LF, Akpotaire O, Goodwin RD, Brown ES. Asthma and depression: the Cooper Center Longitudinal Study. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2014;112(5):432-6.

28. Ahmadiafshar A, Ghoreishi A, Afkhami Ardakani S, Khoshnevisasl P, Faghihzadeh S, Nickmehr P. The High Prevalence of Depression Among Adolescents With Asthma in Iran. Psychosomatic medicine. 2016;78(1):113-4.

29. Delmas MC, Guignon N, Chee CC, Fuhrman C, Herbet JB, Gonzalez L. Asthma and major depressive episode in adolescents in France. The Journal of asthma : official journal of the Association for the Care of Asthma. 2011;48(6):640-6.

30. Jiang M, Qin P, Yang X. Comorbidity between depression and asthma via immune-inflammatory pathways: a meta-analysis. J Affect Disord. 2014;166:22-9.

31. Van Lieshout RJ, MacQueen G. Psychological Factors in Asthma. Allergy, Asthma, and Clinical Immunology : Official Journal of the Canadian Society of Allergy and Clinical Immunology. 2008;4(1):12-28.

32. Yang SN, Shen LJ, Ping T, Wang YC, Chien CW. The delivery mode and seasonal variation are associated with the development of postpartum depression. Journal of Affective Disorders. 2011;132(1-2):158-64.

33. National Heart LaBI: Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma; in National Asthma Education and Prevention Program. 2007:pp 1-417.

34. Global Initiative for Asthma: Global strategy for asthma management and prevention (updated 2009). 2009.

35. Braman SS. The global burden of asthma. Chest. 2006;130(1 Suppl):4s-12s.

36. Anandan C, Nurmatov U, van Schayck OC, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. Allergy. 2010;65(2):152-67.

37. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy. 2004;59(5):469-78.

38. Statistics Canada. Asthma, by sex, provinces and territories (Percent). 2016. Available from: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health50b-eng.htm.

39. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. The Journal of allergy and clinical immunology. 2005;115(1):34-46.

40. Kulig M, Luck W, Lau S, Niggemann B, Bergmann R, Klettke U, et al. Effect of pre- and postnatal tobacco smoke exposure on specific sensitization to food and inhalant allergens

during the first 3 years of life. Multicenter Allergy Study Group, Germany. Allergy. 1999;54(3):220-8.

41. Iikura Y, Naspitz CK, Mikawa H, Talaricoficho S, Baba M, Sole D, et al. Prevention of asthma by ketotifen in infants with atopic dermatitis. Annals of allergy. 1992;68(3):233-6.

42. Harding SM. Acid reflux and asthma. Current opinion in pulmonary medicine. 2003;9(1):42-5.

43. Kwon HL, Triche EW, Belanger K, Bracken MB. The epidemiology of asthma during pregnancy: prevalence, diagnosis, and symptoms. Immunology and allergy clinics of North America. 2006;26(1):29-62.

44. Weiss KB, Gergen PJ, Wagener DK. Breathing better or wheezing worse? The changing epidemiology of asthma morbidity and mortality. Annual review of public health. 1993;14:491-513.

45. Mannino DM, Homa DM, Pertowski CA, Ashizawa A, Nixon LL, Johnson CA, et al. Surveillance for asthma--United States, 1960-1995. MMWR CDC surveillance summaries : Morbidity and mortality weekly report CDC surveillance summaries. 1998;47(1):1-27.

46. Murphy VE, Namazy JA, Powell H, Schatz M, Chambers C, Attia J, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. BJOG : an international journal of obstetrics and gynaecology. 2011;118(11):1314-23.

47. Rey E, Boulet LP. Asthma in pregnancy. BMJ (Clinical research ed). 2007;334(7593):582-5.

48. Blais L, Kettani FZ, Elftouh N, Forget A. Effect of maternal asthma on the risk of specific congenital malformations: A population-based cohort study. Birth defects research Part A, Clinical and molecular teratology. 2010;88(4):216-22.

49. Liu S, Wen SW, Demissie K, Marcoux S, Kramer MS. Maternal asthma and pregnancy outcomes: a retrospective cohort study. American journal of obstetrics and gynecology. 2001;184(2):90-6.

50. Firoozi F, Lemiere C, Beauchesne MF, Perreault S, Forget A, Blais L. Impact of maternal asthma on perinatal outcomes: a two-stage sampling cohort study. European journal of epidemiology. 2012;27(3):205-14.

51. Rejno G, Lundholm C, Gong T, Larsson K, Saltvedt S, Almqvist C. Asthma during pregnancy in a population-based study--pregnancy complications and adverse perinatal outcomes. PLoS One. 2014;9(8):e104755.

52. Yawn B, Knudtson M. Treating asthma and comorbid allergic rhinitis in pregnancy. Journal of the American Board of Family Medicine : JABFM. 2007;20(3):289-98.

53. Gluck JC. The change of asthma course during pregnancy. Clinical reviews in allergy & immunology. 2004;26(3):171-80.

54. Juniper, EF, NM. Effect of pregnancy on asthma: a critical appraisal of the literature. 1993:223-49.

55. Gluck JC, Gluck P. The effects of pregnancy on asthma: a prospective study. Annals of allergy. 1976;37(3):164-8.

56. Holbreich M. Asthma and other allergic disorders in pregnancy. American family physician. 1982;25(3):187-92.

57. Blaiss MS. Management of rhinitis and asthma in pregnancy. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2003;90(6 Suppl 3):16-22.

58. Cox JL, Murray D, Chapman G. A controlled study of the onset, duration and prevalence of postnatal depression. The British journal of psychiatry : the journal of mental science. 1993;163:27-31.

59. Watson JP, Elliott SA, Rugg AJ, Brough DI. Psychiatric disorder in pregnancy and the first postnatal year. The British journal of psychiatry : the journal of mental science. 1984;144:453-62.

60. Verreault N, Da Costa D, Marchand A, Ireland K, Dritsa M, Khalife S. Rates and risk factors associated with depressive symptoms during pregnancy and with postpartum onset. Journal of psychosomatic obstetrics and gynaecology. 2014;35(3):84-91.

61. Lanes A, Kuk JL, Tamim H. Prevalence and characteristics of postpartum depression symptomatology among Canadian women: a cross-sectional study. BMC public health. 2011;11:302.

62. Wisner KL, Parry BL, Piontek CM. Clinical practice. Postpartum depression. The New England journal of medicine. 2002;347(3):194-9.

63. Beck CT, Reynolds MA, Rutowski P. Maternity blues and postpartum depression. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN / NAACOG. 1992;21(4):287-93.

64. Mills EP, Finchilescu G, Lea SJ. Postnatal depression--an examination of psychosocial factors. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 1995;85(2):99-105.

65. Ritter C, Hobfoll SE, Lavin J, Cameron RP, Hulsizer MR. Stress, psychosocial resources, and depressive symptomatology during pregnancy in low-income, inner-city women. Health psychology : official journal of the Division of Health Psychology, American Psychological Association. 2000;19(6):576-85.

66. Loerbroks A, Herr RM, Subramanian S, Bosch JA. The association of asthma and wheezing with major depressive episodes: an analysis of 245 727 women and men from 57 countries. International journal of epidemiology. 2012;41(5):1436-44.

67. Goldney RD, Ruffin R, Fisher LJ, Wilson DH. Asthma symptoms associated with depression and lower quality of life: a population survey. The Medical journal of Australia. 2003;178(9):437-41.

68. Walters P, Schofield P, Howard L, Ashworth M, Tylee A. The relationship between asthma and depression in primary care patients: a historical cohort and nested case control study. PLoS One. 2011;6(6):e20750.

69. Scott KM, Von Korff M, Ormel J, Zhang MY, Bruffaerts R, Alonso J, et al. Mental disorders among adults with asthma: results from the World Mental Health Survey. General hospital psychiatry. 2007;29(2):123-33.

70. de Miguel Diez J, Hernandez Barrera V, Puente Maestu L, Carrasco Garrido P, Gomez Garcia T, Jimenez Garcia R. Psychiatric comorbidity in asthma patients. Associated factors. The Journal of asthma : official journal of the Association for the Care of Asthma. 2011;48(3):253-8.

71. Brunner WM, Schreiner PJ, Sood A, Jacobs DR, Jr. Depression and risk of incident asthma in adults. The CARDIA study. American journal of respiratory and critical care medicine. 2014;189(9):1044-51.

72. Nazareth I, King M, Davies S. Care of schizophrenia in general practice: the general practitioner and the patient. The British Journal of General Practice. 1995;45(396):343-7.

73. Tata LJ, Lewis SA, McKeever TM, Smith CJ, Doyle P, Smeeth L, et al. A comprehensive analysis of adverse obstetric and pediatric complications in women with asthma. American journal of respiratory and critical care medicine. 2007;175(10):991-7.

74. Hansell A, Hollowell J, Nichols T, McNiece R, Strachan D. Use of the General Practice Research Database (GPRD) for respiratory epidemiology: a comparison with the 4th Morbidity Survey in General Practice (MSGP4). Thorax. 1999;54(5):413-9.

75. Stevens A, Raftery J. Health Care Needs Assessment: The Epidemiologically Based Needs Assessment Reviews. Oxford: Radcliffe Medical Press. 1994.

76. van den Bemt L, Luijks H, Bor H, Termeer E, Lucassen P, Schermer T. Are asthma patients at increased risk of clinical depression? A longitudinal cohort study. Journal of Asthma. 2016;53(1):43-9.

77. Piek E, Nolen WA, van der Meer K, Joling KJ, Kollen BJ, Penninx BW, et al. Determinants of (non-)recognition of depression by general practitioners: results of the Netherlands Study of Depression and Anxiety. J Affect Disord. 2012;138(3):397-404.

78. Goodwin RD, Fergusson DM, Horwood LJ. Asthma and depressive and anxiety disorders among young persons in the community. Psychological medicine. 2004;34(8):1465-74.

79. Koutra K, Vassilaki M, Georgiou V, Koutis A, Bitsios P, Chatzi L, et al. Antenatal maternal mental health as determinant of postpartum depression in a population based mother-child cohort (Rhea Study) in Crete, Greece. Social psychiatry and psychiatric epidemiology. 2014;49(5):711-21.

80. Milgrom J, Gemmill AW, Bilszta JL, Hayes B, Barnett B, Brooks J, et al. Antenatal risk factors for postnatal depression: a large prospective study. J Affect Disord. 2008;108(1-2):147-57.

81. Siu BW, Leung SS, Ip P, Hung SF, O'Hara MW. Antenatal risk factors for postnatal depression: a prospective study of Chinese women at maternal and child health centres. BMC psychiatry. 2012;12:22.

82. Gaillard A, Le Strat Y, Mandelbrot L, Keita H, Dubertret C. Predictors of postpartum depression: prospective study of 264 women followed during pregnancy and postpartum. Psychiatry research. 2014;215(2):341-6.

83. Woolhouse H, Gartland D, Mensah F, Brown SJ. Maternal depression from early pregnancy to 4 years postpartum in a prospective pregnancy cohort study: Implications for primary health care. BJOG: An International Journal of Obstetrics and Gynaecology. 2015;122(3):312-21.

84. Lee AM, Lam SK, Sze Mun Lau SM, Chong CS, Chui HW, Fong DY. Prevalence, course, and risk factors for antenatal anxiety and depression. Obstetrics and gynecology. 2007;110(5):1102-12.

85. Heron J, O'Connor TG, Evans J, Golding J, Glover V. The course of anxiety and depression through pregnancy and the postpartum in a community sample. J Affect Disord. 2004;80(1):65-73.

86. Park JH, Karmaus W, Zhang H. Prevalence of and Risk Factors for Depressive Symptoms in Korean Women throughout Pregnancy and in Postpartum Period. Asian nursing research. 2015;9(3):219-25.

87. Hamdan A, Tamim H. Psychosocial risk and protective factors for postpartum depression in the United Arab Emirates. Archives of women's mental health. 2011;14(2):125-33.

88. Golding J, Pembrey M, Jones R. ALSPAC--the Avon Longitudinal Study of Parents and Children. I. Study methodology. Paediatr Perinat Epidemiol. 2001;15(1):74-87.

89. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. The British journal of psychiatry : the journal of mental science. 1987;150:782-6.

90. Koutra K, Vassilaki M, Georgiou V, Koutis A, Bitsios P, Chatzi L, et al. Antenatal maternal mental health as determinant of postpartum depression in a population based mother-child cohort (Rhea Study) in Crete, Greece. Social psychiatry and psychiatric epidemiology. 2014;49(5):711-21.

91. Kheirabadi GR, Maracy MR, Barekatain M, Salehi M, Sadri GH, Kelishadi M, et al. Risk factors of postpartum depression in rural areas of Isfahan Province, Iran. Archives of Iranian medicine. 2009;12(5):461-7.

92. Nakku JE, Nakasi G, Mirembe F. Postpartum major depression at six weeks in primary health care: prevalence and associated factors. African health sciences. 2006;6(4):207-14.

93. Vigod SN, Tarasoff LA, Bryja B, Dennis CL, Yudin MH, Ross LE. Relation between place of residence and postpartum depression. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2013;185(13):1129-35.

94. Rubertsson C, Wickberg B, Gustavsson P, Radestad I. Depressive symptoms in early pregnancy, two months and one year postpartum-prevalence and psychosocial risk factors in a national Swedish sample. Archives of women's mental health. 2005;8(2):97-104.

95. Eastwood JG, Jalaludin BB, Kemp LA, Phung HN, Barnett BE. Relationship of postnatal depressive symptoms to infant temperament, maternal expectations, social support and other potential risk factors: findings from a large Australian cross-sectional study. BMC pregnancy and childbirth. 2012;12:148.

96. Kozinszky Z, Dudas RB, Csatordai S, Devosa I, Toth E, Szabo D, et al. Social dynamics of postpartum depression: a population-based screening in South-Eastern Hungary. Social psychiatry and psychiatric epidemiology. 2011;46(5):413-23.

97. Savitz DA, Stein CR, Ye F, Kellerman L, Silverman M. The epidemiology of hospitalized postpartum depression in New York State, 1995-2004. Annals of epidemiology. 2011;21(6):399-406.

98. Ali NS, Ali BS, Azam IS. Post partum anxiety and depression in peri-urban communities of Karachi, Pakistan: a quasi-experimental study. BMC public health. 2009;9:384.

99. Gausia K, Fisher C, Ali M, Oosthuizen J. Magnitude and contributory factors of postnatal depression: a community-based cohort study from a rural subdistrict of Bangladesh. Psychological medicine. 2009;39(6):999-1007.

100. Aydin N, Inandi T, Karabulut N. Depression and associated factors among women within their first postnatal year in Erzurum province in eastern Turkey. Women & health. 2005;41(2):1-12.

101. Ho-Yen SD, Bondevik GT, Eberhard-Gran M, Bjorvatn B. Factors associated with depressive symptoms among postnatal women in Nepal. Acta obstetricia et gynecologica Scandinavica. 2007;86(3):291-7.

102. Kozhimannil KB, Pereira MA, Harlow BL. Association between diabetes and perinatal depression among low-income mothers. Jama. 2009;301(8):842-7.

103. Kim HG, Geppert J, Quan T, Bracha Y, Lupo V, Cutts DB. Screening for postpartum depression among low-income mothers using an interactive voice response system. Maternal and child health journal. 2012;16(4):921-8.

104. Chee CY, Lee DT, Chong YS, Tan LK, Ng TP, Fones CS. Confinement and other psychosocial factors in perinatal depression: a transcultural study in Singapore. J Affect Disord. 2005;89(1-3):157-66.

105. Raisanen S, Lehto SM, Nielsen HS, Gissler M, Kramer MR, Heinonen S. Fear of childbirth predicts postpartum depression: a population-based analysis of 511 422 singleton births in Finland. BMJ Open. 2013;3(11):e004047.

106. LaCoursiere DY, Barrett-Connor E, O'Hara MW, Hutton A, Varner MW. The association between prepregnancy obesity and screening positive for postpartum depression. BJOG : an international journal of obstetrics and gynaecology. 2010;117(8):1011-8.

107. Johnstone SJ, Boyce PM, Hickey AR, Morris-Yatees AD, Harris MG. Obstetric risk factors for postnatal depression in urban and rural community samples. The Australian and New Zealand journal of psychiatry. 2001;35(1):69-74.

108. Ahmed HM, Alalaf SK, Al-Tawil NG. Screening for postpartum depression using Kurdish version of Edinburgh postnatal depression scale. Archives of gynecology and obstetrics. 2012;285(5):1249-55.

109. Kettunen P, Koistinen E, Hintikka J. Is postpartum depression a homogenous disorder: time of onset, severity, symptoms and hopelessness in relation to the course of depression. BMC pregnancy and childbirth. 2014;14:402.

110. Austin MP, Tully L, Parker G. Examining the relationship between antenatal anxiety and postnatal depression. J Affect Disord. 2007;101(1-3):169-74.

111. Grant KA, McMahon C, Austin MP. Maternal anxiety during the transition to parenthood: a prospective study. J Affect Disord. 2008;108(1-2):101-11.

112. Goshtasebi A, Alizadeh M, Gandevani SB. Association between maternal anaemia and postpartum depression in an urban sample of pregnant women in Iran. Journal of health, population, and nutrition. 2013;31(3):398-402.

113. Barbadoro P, Cotichelli G, Chiatti C, Simonetti ML, Marigliano A, Di Stanislao F, et al. Socio-economic determinants and self-reported depressive symptoms during postpartum period. Women & health. 2012;52(4):352-68.

114. Dennis CL, Janssen PA, Singer J. Identifying women at-risk for postpartum depression in the immediate postpartum period. Acta psychiatrica Scandinavica. 2004;110(5):338-46.

115. Josefsson A, Angelsioo L, Berg G, Ekstrom CM, Gunnervik C, Nordin C, et al. Obstetric, somatic, and demographic risk factors for postpartum depressive symptoms. Obstetrics and gynecology. 2002;99(2):223-8.

116. Homish GG, Cornelius JR, Richardson GA, Day NL. Antenatal risk factors associated with postpartum comorbid alcohol use and depressive symptomatology. Alcoholism, clinical and experimental research. 2004;28(8):1242-8.

117. Dietz PM, Williams SB, Callaghan WM, Bachman DJ, Whitlock EP, Hornbrook MC. Clinically identified maternal depression before, during, and after pregnancies ending in live births. The American journal of psychiatry. 2007;164(10):1515-20.

118. Rahman A, Iqbal Z, Bunn J, Lovel H, Harrington R. Impact of maternal depression on infant nutritional status and illness: a cohort study. Archives of general psychiatry. 2004;61(9):946-52.

119. Demirchyan A, Petrosyan D, Armenian HK. Rate and predictors of postpartum depression in a 22-year follow-up of a cohort of earthquake survivors in Armenia. Archives of women's mental health. 2014;17(3):229-37.

120. Blais L, Kettani FZ, Forget A, Beauchesne MF, Lemiere C. Asthma exacerbations during the first trimester of pregnancy and congenital malformations: revisiting the association in a large representative cohort. Thorax. 2015;70(7):647-52.

121. Eltonsy S, Forget A, Beauchesne MF, Blais L. Risk of congenital malformations for asthmatic pregnant women using a long-acting beta(2)-agonist and inhaled corticosteroid combination versus higher-dose inhaled corticosteroid monotherapy. The Journal of allergy and clinical immunology. 2015;135(1):123-30.

122. Vilain A, Otis S, Forget A, Blais L. Agreement between administrative databases and medical charts for pregnancy-related variables among asthmatic women. Pharmacoepidemiology and drug safety. 2008;17(4):345-53.

123. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. Canadian respiratory journal : journal of the Canadian Thoracic Society. 2009;16(6):183-8.

124. Blais L, Lemiere C, Menzies D, Berbiche D. Validity of asthma diagnoses recorded in the Medical Services database of Quebec. Pharmacoepidemiology and drug safety. 2006;15(4):245-52.

125. Statistics Canada. Mental disorders, conditions, and ICD-9 and ICD-10-CA codes. 2015. Available from: http://www.statcan.gc.ca/pub/82-622-x/2011006/tbl/tbla-eng.htm.

126. Fiest KM, Jette N, Quan H, St Germaine-Smith C, Metcalfe A, Patten SB, et al. Systematic review and assessment of validated case definitions for depression in administrative data. BMC psychiatry. 2014;14:289.

127. Rothman KJ, S G. Modern epidemiology. ed Second, Lippincott Williams & Wilkins,. 2006.

128. Rothman K. Epidemiology, an introduction. Oxford, Oxford University Press,. 2002.

129. Hennekens CH, Buring JE, SL M. Epidemiology in medicine. ed 1st ed, Philadelphia, Lippincott Williams & Wilkins,. 1987.

130. MacKinnon DP, Fairchild AJ, Fritz MS. Mediation Analysis. Annual review of psychology. 2007;58:593.

131. Segre LS, O'Hara MW, Arndt S, Stuart S. The prevalence of postpartum depression: the relative significance of three social status indices. Social psychiatry and psychiatric epidemiology. 2007;42(4):316-21.

132. Abiodun OA. Postnatal depression in primary care populations in Nigeria. General hospital psychiatry. 2006;28(2):133-6.

133. MacKinnon DP, Krull JL, Lockwood CM. Equivalence of the Mediation, Confounding and Suppression Effect. Prevention science : the official journal of the Society for Prevention Research. 2000;1(4):173.

134. Ballinger GA. Using Generalized Estimating Equations for Longitudinal Data Analysis. SAGE Journals Online. 2004;7(2):127-50.

135. Zeger SL, Liang K-Y, Albert PS. Models for Longitudinal Data: A Generalized Estimating Equation Approach. Biometrics. 1988;44(4):1049-60.

136. Cutrona CE. Social support and stress in the transition to parenthood. Journal of abnormal psychology. 1984;93(4):378-90.

137. Jones HW, Venis JA. Identification and classification of postpartum psychiatric disorders. Journal of psychosocial nursing and mental health services. 2001;39(12):23-30.

138. Lam RW, Kennedy SH, Grigoriadis S, McIntyre RS, Milev R, Ramasubbu R, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. Journal of Affective Disorders. 2009;117:S26–S43.

139. Eagan TM, Gulsvik A, Eide GE, Bakke PS. The effect of educational level on the incidence of asthma and respiratory symptoms. Respiratory medicine. 2004;98(8):730-6.

140. Loerbroks A, Apfelbacher CJ, Bosch JA, Sturmer T. Depressive symptoms, social support, and risk of adult asthma in a population-based cohort study. Psychosomatic medicine. 2010;72(3):309-15.

141. Chun TH, Weitzen SH, Fritz GK. The asthma/mental health nexus in a population-based sample of the United States. Chest. 2008;134(6):1176-82.

142. Ehrlich SF, Quesenberry CP, Van Den Eeden SK, Shan J, Ferrara A. Patients Diagnosed With Diabetes Are at Increased Risk for Asthma, Chronic Obstructive Pulmonary Disease, Pulmonary Fibrosis, and Pneumonia but Not Lung Cancer. Diabetes Care. 2010;33(1):55-60.

143. von Maffei J, Beckett WS, Belanger K, Triche E, Zhang H, Machung JF, et al. Risk factors for asthma prevalence among urban and nonurban African American children. The Journal of asthma : official journal of the Association for the Care of Asthma. 2001;38(7):555-64.

144. Elenkov IJ, Webster EL, Torpy DJ, Chrousos GP. Stress, corticotropin-releasing hormone, glucocorticoids, and the immune/inflammatory response: acute and chronic effects. Annals of the New York Academy of Sciences. 1999;876:1-11; discussion -3.

145. Wamboldt MZ, Weintraub P, Krafchick D, Wamboldt FS. Psychiatric family history in adolescents with severe asthma. Journal of the American Academy of Child and Adolescent Psychiatry. 1996;35(8):1042-9.

146. Leung DY, Spahn JD, Szefler SJ. Immunologic basis and management of steroid-resistant asthma. Allergy and asthma proceedings : the official journal of regional and state allergy societies. 1999;20(1):9-14.

147. Bumbacea D, Campbell D, Nguyen L, Carr D, Barnes PJ, Robinson D, et al. Parameters associated with persistent airflow obstruction in chronic severe asthma. The European respiratory journal. 2004;24(1):122-8.

148. Pariante CM, Miller AH. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. Biological psychiatry. 2001;49(5):391-404.

149. Banki CM, Karmacsi L, Bissette G, Nemeroff CB. CSF corticotropin-releasing hormone and somatostatin in major depression: response to antidepressant treatment and relapse. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 1992;2(2):107-13.

150. Wong ML, Kling MA, Munson PJ, Listwak S, Licinio J, Prolo P, et al. Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: Relation to hypercortisolism and corticotropin-releasing hormone. Proceedings of the National Academy of Sciences of the United States of America. 2000;97(1):325-30.

151. Roy A, Pickar D, Paul S, Doran A, Chrousos GP, Gold PW. CSF corticotropin-releasing hormone in depressed patients and normal control subjects. The American journal of psychiatry. 1987;144(5):641-5.

152. Watkins LR, Maier SF. Immune regulation of central nervous system functions: from sickness responses to pathological pain. Journal of internal medicine. 2005;257(2):139-55.

153. Leung KB, Flint KC, Brostoff J, Hudspith BN, Johnson NM, Lau HY, et al. Effects of sodium cromoglycate and nedocromil sodium on histamine secretion from human lung mast cells. Thorax. 1988;43(10):756-61.

154. Rubinsztein JS, Michael A, Paykel ES, Sahakian BJ. Cognitive impairment in remission in bipolar affective disorder. Psychological medicine. 2000;30(5):1025-36.

155. Lemelin S, Baruch P, Vincent A, Laplante L, Everett J, Vincent P. Attention disturbance in clinical depression. Deficient distractor inhibition or processing resource deficit? The Journal of nervous and mental disease. 1996;184(2):114-21.

156. Akyol O, Zoroglu SS, Armutcu F, Sahin S, Gurel A. Nitric oxide as a physiopathological factor in neuropsychiatric disorders. In vivo (Athens, Greece). 2004;18(3):377-90.

157. McLeod TM, Lopez-Figueroa AL, Lopez-Figueroa MO. Nitric oxide, stress, and depression. Psychopharmacology bulletin. 2001;35(1):24-41.

158. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood P, et al. Self-management education and regular practitioner review for adults with asthma. The Cochrane database of systematic reviews. 2003(1):Cd001117.

159. Kolbe J, Vamos M, Fergusson W, Elkind G, Garrett J. Differential influences on asthma self-management knowledge and self-management behavior in acute severe asthma. Chest. 1996;110(6):1463-8.

160. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. Journal of clinical epidemiology. 1995;48(8):999-1009.

161. Blais L, Lemiere C, D B. Validation of asthma diagnostic codes in the administrative health databases of Quebec, Canada. 2004:p S32.

162. Blais L, Forget A. Asthma exacerbations during the first trimester of pregnancy and the risk of congenital malformations among asthmatic women. The Journal of allergy and clinical immunology. 2008;121(6):1379-84, 84.e1.

163. Martel MJ, Rey E, Beauchesne MF, Perreault S, Lefebvre G, Forget A, et al. Use of inhaled corticosteroids during pregnancy and risk of pregnancy induced hypertension: nested case-control study. BMJ (Clinical research ed). 2005;330(7485):230.

164. Martel MJ, Rey E, Beauchesne MF, Perreault S, Forget A, Maghni K, et al. Use of short-acting beta2-agonists during pregnancy and the risk of pregnancy-induced hypertension. The Journal of allergy and clinical immunology. 2007;119(3):576-82.

165. Blais L, Beauchesne MF. Use of inhaled corticosteroids following discharge from an emergency department for an acute exacerbation of asthma. Thorax. 2004;59(11):943-7.

166. Gordis L. Epidemiology. ed 3rd ed, Philadelphia, Pa, Elsevier Saunders. 2004.

167. Mausner JS, Bahn AK. Epidemiology. An introductory text1974.

168. Magnus MC, DeRoo LA, Håberg SE, Magnus P, Nafstad P, Nystad W, et al. Prospective Study of Maternal Alcohol Intake During Pregnancy or Lactation and Risk of Childhood Asthma: The Norwegian Mother and Child Cohort Study. Alcoholism, clinical and experimental research. 2014;38(4):1002-11.

169. Hasler G, Gergen PJ, Kleinbaum DG, Ajdacic V, Gamma A, Eich D, et al. Asthma and Panic in Young Adults: A 20-Year Prospective Community Study. American journal of respiratory and critical care medicine. 2005;171(11):1224-30.

170. Hafkamp-de Groen E, Sonnenschein-van der Voort AMM, Mackenbach JP, Duijts L, Jaddoe VWV, Moll Hë A, et al. Socioeconomic and Sociodemographic Factors Associated with Asthma Related Outcomes in Early Childhood: The Generation R Study. PLoS One. 2013;8(11).

171. Subramanian SV, Ackerson LK, Subramanyam MA, Wright RJ. Domestic violence is associated with adult and childhood asthma prevalence in India. International journal of epidemiology. 2007;36(3):569-79.

172. Coogan PF, Wise LA, O'Connor GT, Brown TA, Palmer JR, Rosenberg L. Abuse during Childhood and Adolescence and Risk of Adult-Onset Asthma in African American Women. The Journal of allergy and clinical immunology. 2013;131(4):1058-63.

173. Harpsoe MC, Basit S, Bager P, Wohlfahrt J, Benn CS, Nohr EA, et al. Maternal obesity, gestational weight gain, and risk of asthma and atopic disease in offspring: a study within the Danish National Birth Cohort. The Journal of allergy and clinical immunology. 2013;131(4):1033-40.

174. Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics. 2012;129(4):735-44.

175. Vazquez-Nava F, Gil-Lara B, Cruz-Torres L, Vazquez-Rodriguez CF, Vazquez-Rodriguez EM, Felizardo-Avalos J, et al. [Association between unplanned pregnancy and adolescence onset asthma]. Revista alergia Mexico (Tecamachalco, Puebla, Mexico : 1993). 2013;60(4):152-60.

176. Oliveti JF, Kercsmar CM, Redline S. Pre- and perinatal risk factors for asthma in inner city African-American children. Am J Epidemiol. 1996;143(6):570-7.

177. Dennis CL, Dowswell T. Psychosocial and psychological interventions for preventing postpartum depression. The Cochrane database of systematic reviews. 2013(2):Cd001134.